CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204629Orig1s005

Trade Name: **JARDIANCE**

Generic Name: Empagliflozin

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date: 03/18/2016

Indications: JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204629/S-005

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director, Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 20, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jardiance (empagliflozin) tablets.

This "Prior Approval" supplemental new drug application proposes to amend the Jardiance prescribing information with new information describing the results of Study 1276.1 entitled, "A 24-week phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug-naïve patients with type 2 diabetes mellitus." Additional changes proposed in this supplement include new text describing results of a UGT interaction study.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your supplemental application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Michael G. White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
03/18/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JARDIANCE safely and effectively. See full prescribing information for JARDIANCE.

JARDIANCE® (empagliflozin) tablets, for oral use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.2, 5.4) 12/2015

----------INDICATIONS AND USAGE----------

JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitation of Use:

- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1.1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dose of JARDIANCE is 10 mg once daily, taken in the morning, with or without food (2.1)
- Dose may be increased to 25 mg once daily (2.1)
- Assess renal function before initiating JARDIANCE. Do not initiate JARDIANCE if eGFR is below 45 mL/min/1.73 m^2 (2.2)
- Discontinue JARDIANCE if eGFR falls persistently below 45 mL/min/1.73 m^2 (2 2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 10 mg, 25 mg (3)

----------CONTRAINDICATIONS----------

- History of serious hypersensitivity reaction to JARDIANCE (4)
- Severe renal impairment, end-stage renal disease, or dialysis (4)

----------WARNINGS AND PRECAUTIONS----------

- *Hypotension* Before initiating JARDIANCE assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.1)
- *Ketoacidosis* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue JARDIANCE, evaluate and treat promptly. Before initiating JARDIANCE, consider risk factors for ketoacidosis. Patients on JARDIANCE may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.2)
- *Impairment in renal function* Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR below 60 mL/min/1.73 m^2 (5 3)
- *Urosepsis and Pyelonephritis* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.4)
- *Hypoglycemia* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating JARDIANCE (5.5)
- *Genital mycotic infections* Monitor and treat as appropriate (5.6)
- *Increased LDL-C* Monitor and treat as appropriate (5.7)
- *Macrovascular outcomes*: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JARDIANCE (5.8)

----------ADVERSE REACTIONS----------

- The most common adverse reactions associated with JARDIANCE (5% or greater incidence) were urinary tract infections and female genital mycotic infections (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy* No adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- *Nursing mothers* Discontinue JARDIANCE or discontinue nursing (8.3)
- *Geriatric patients* Higher incidence of adverse reactions related to volume depletion and reduced renal function (5.1, 5.3, 8.5)
- *Patients with renal impairment* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

JARDIANCE is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14)]*.

1.1 Limitation of Use

JARDIANCE is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of JARDIANCE is 10 mg once daily in the morning, taken with or without food. In patients tolerating JARDIANCE, the dose may be increased to 25 mg *[see Clinical Studies (14)]*.

In patients with volume depletion, correcting this condition prior to initiation of JARDIANCE is recommended *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5), and Patient Counseling Information (17)]*.

2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of JARDIANCE and periodically thereafter.

JARDIANCE should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.

No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.

JARDIANCE should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (5.1, 5.3), and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

- JARDIANCE (empagliflozin) 10 mg tablets are pale yellow, round, biconvex and bevel-edged, film-coated tablets debossed with “S 10” on one side and the Boehringer Ingelheim company symbol on the other side.
- JARDIANCE (empagliflozin) 25 mg tablets are pale yellow, oval, biconvex, film-coated tablets debossed with “S 25” on one side and the Boehringer Ingelheim company symbol on the other side.

4 CONTRAINDICATIONS

- History of serious hypersensitivity reaction to JARDIANCE.
- Severe renal impairment, end-stage renal disease, or dialysis *[see Use in Specific Populations (8.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE *[see Adverse Reactions (6.1)]* particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating JARDIANCE, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected *[see Use in Specific Populations (8.5)]*.

5.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including JARDIANCE. JARDIANCE is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with JARDIANCE who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with JARDIANCE may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDIANCE should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating JARDIANCE, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with JARDIANCE consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.3 Impairment in Renal Function

JARDIANCE increases serum creatinine and decreases eGFR *[see Adverse Reactions (6.1)]*. The risk of impaired renal function with JARDIANCE is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients *[see Use in Specific Populations* (*8.5, 8.6)]*. Renal function should be evaluated prior to initiating JARDIANCE and periodically thereafter.

5.4 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including JARDIANCE. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6)]*.

5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE.

5.6 Genital Mycotic Infections
JARDIANCE increases the risk for genital mycotic infections *[see Adverse Reactions (6.1)]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate.

5.7 Increased Low-Density Lipoprotein Cholesterol (LDL-C)
Increases in LDL-C can occur with JARDIANCE *[see Adverse Reactions (6.1)]*. Monitor and treat as appropriate.

5.8 Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JARDIANCE or any other antidiabetic drug.

6 ADVERSE REACTIONS
The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions (5.1)]*
- Ketoacidosis *[see Warnings and Precautions (5.2)]*
- Impairment in Renal Function *[see Warnings and Precautions (5.3)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.4)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.5)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6)]*
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Placebo-Controlled Trials evaluating JARDIANCE 10 and 25 mg
The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin. JARDIANCE was used as monotherapy in one trial and as add-on therapy in four trials *[see Clinical Studies (14)]*.

These data reflect exposure of 1976 patients to JARDIANCE with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), JARDIANCE 10 mg (N=999), or JARDIANCE 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m^2).

Table 1 shows common adverse reactions (excluding hypoglycemia) associated with the use of JARDIANCE. The adverse reactions were not present at baseline, occurred more commonly on JARDIANCE than on placebo and occurred in greater than or equal to 2% of patients treated with JARDIANCE 10 mg or JARDIANCE 25 mg.

Table 1 Adverse Reactions Reported in ≥2% of Patients Treated with JARDIANCE and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of JARDIANCE Monotherapy or Combination Therapy

	Number (%) of Patients		
	Placebo N=995	**JARDIANCE 10 mg N=999**	**JARDIANCE 25 mg N=977**
Urinary tract infection[a]	7.6%	9.3%	7.6%
Female genital mycotic infections[b]	1.5%	5.4%	6.4%
Upper respiratory tract infection	3.8%	3.1%	4.0%
Increased urination[c]	1.0%	3.4%	3.2%
Dyslipidemia	3.4%	3.9%	2.9%
Arthralgia	2.2%	2.4%	2.3%
Male genital mycotic infections[d]	0.4%	3.1%	1.6%
Nausea	1.4%	2.3%	1.1%

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis
[b]Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), JARDIANCE 10 mg (N=443), JARDIANCE 25 mg (N=420).
[c]Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia
[d]Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), JARDIANCE 10 mg (N=556), JARDIANCE 25 mg (N=557).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

Volume Depletion
JARDIANCE causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg respectively. JARDIANCE may increase the risk of hypotension in patients at risk for volume contraction *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.5, 8.6)]*.

Increased Urination
In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on JARDIANCE than on placebo (see Table 1). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

Impairment in Renal Function
Use of JARDIANCE was associated with increases in serum creatinine and decreases in eGFR (see Table 2). Patients with moderate renal impairment at baseline had larger mean changes *[see Warnings and Precautions (5.3)* and *Use in Specific Populations (8.5, 8.6)]*.

Table 2 Changes from Baseline in Serum Creatinine and eGFR in the Pool of Four 24-week Placebo-Controlled Studies and Renal Impairment Study

		Pool of 24-Week Placebo-Controlled Studies		
		Placebo	**JARDIANCE 10 mg**	**JARDIANCE 25 mg**
Baseline Mean	N	825	830	822
	Creatinine (mg/dL)	0.84	0.85	0.85
	eGFR (mL/min/1.73 m^2)	87.3	87.1	87.8
Week 12 Change	N	771	797	783
	Creatinine (mg/dL)	0.00	0.02	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-1.3	-1.4
Week 24 Change	N	708	769	754
	Creatinine (mg/dL)	0.00	0.01	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-0.6	-1.4
		Moderate Renal Impairment[a]		
		Placebo		**JARDIANCE 25 mg**
Baseline	N	187	--	187
	Creatinine (mg/dL)	1.49	--	1.46
	eGFR (mL/min/1.73 m^2)	44.3	--	45.4
Week 12 Change	N	176	--	179
	Creatinine (mg/dL)	0.01	--	0.12
	eGFR (mL/min/1.73 m^2)	0.1	--	-3.8
Week 24 Change	N	170	--	171
	Creatinine (mg/dL)	0.01	--	0.10
	eGFR (mL/min/1.73 m^2)	0.2	--	-3.2
Week 52 Change	N	164	--	162
	Creatinine (mg/dL)	0.02	--	0.11
	eGFR (mL/min/1.73 m^2)	-0.3	--	-2.8

[a]Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 m^2

Hypoglycemia
The incidence of hypoglycemia by study is shown in Table 3. The incidence of hypoglycemia increased when JARDIANCE was administered with insulin or sulfonylurea *[see Warnings and Precautions (5.5)]*.

Table 3 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies

Monotherapy (24 weeks)	**Placebo (n=229)**	**JARDIANCE 10 mg (n=224)**	**JARDIANCE 25 mg (n=223)**
Overall (%)	0.4%	0.4%	0.4%
Severe (%)	0%	0%	0%
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**JARDIANCE 10 mg + Metformin (n=217)**	**JARDIANCE 25 mg + Metformin (n=214)**
Overall (%)	0.5%	1.8%	1.4%
Severe (%)	0%	0%	0%
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)**	**JARDIANCE 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4%	16.1%	11.5%
Severe (%)	0%	0%	0%
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)**	**JARDIANCE 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8%	1.2%	2.4%
Severe (%)	0%	0%	0%
In Combination with Basal Insulin (18 weeks[c])	**Placebo (n=170)**	**JARDIANCE 10 mg (n=169)**	**JARDIANCE 25 mg (n=155)**
Overall (%)	20.6%	19.5%	28.4%
Severe (%)	0%	0%	1.3%
In Combination with MDI Insulin +/- Metformin (18 weeks[c])	**Placebo (n=188)**	**JARDIANCE 10 mg (n=186)**	**JARDIANCE 25 mg (n=189)**
Overall (%)	37.2%	39.8%	41.3%
Severe (%)	0.5%	0.5%	0.5%

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Insulin dose could not be adjusted during the initial 18 week treatment period

Genital Mycotic Infections
In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with JARDIANCE compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either JARDIANCE 10 or 25 mg.

Genital mycotic infections occurred more frequently in female than male patients (see Table 1).

Phimosis occurred more frequently in male patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%).

Urinary Tract Infections
In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with JARDIANCE compared to placebo (see Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.5)]*.

Laboratory Tests
Increase in Low-Density Lipoprotein Cholesterol (LDL-C)
Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with JARDIANCE. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions (5.7)]*. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit
In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in JARDIANCE 10 mg and 2.8% in JARDIANCE 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

6.2 Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of JARDIANCE. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis *[see Warnings and Precautions (5.2)]*
- Urosepsis and pyelonephritis *[see Warnings and Precautions (5.4)]*

7 DRUG INTERACTIONS
7.1 Diuretics
Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion *[see Warnings and Precautions (5.1)]*.

7.2 Insulin or Insulin Secretagogues
Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia *[see Warnings and Precautions (5.5)]*.

7.3 Positive Urine Glucose Test
Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

7.4 Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of JARDIANCE in pregnant women. JARDIANCE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Based on results from animal studies, empagliflozin may affect renal development and maturation. In studies conducted in rats, empagliflozin crosses the placenta and reaches fetal tissues. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

In a juvenile toxicity study in the rat, when empagliflozin was administered to young rats from postnatal day (PND) 21 until PND 90, at doses of 1, 10, 30 and 100 mg/kg/day, increased kidney weights and renal tubular and pelvic dilatation were seen at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13 week drug-free recovery period.

Empagliflozin was not teratogenic in embryo-fetal development studies in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg. At higher doses, causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154 times the 25 mg maximum clinical dose in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139 times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16 times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4 times the 25 mg maximum clinical dose).

8.3 Nursing Mothers

It is not known if JARDIANCE is excreted in human milk. Empagliflozin is secreted in the milk of lactating rats reaching levels up to 5 times higher than that in maternal plasma. Data in juvenile rats directly exposed to empagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation which were not observed after a 13 week drug-free recovery period. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from JARDIANCE, a decision should be made whether to discontinue nursing or to discontinue JARDIANCE, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of JARDIANCE in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No JARDIANCE dosage change is recommended based on age *[see Dosage and Administration (2)]*. A total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. JARDIANCE is expected to have diminished efficacy in elderly patients with renal impairment *[see Use in Specific Populations (8.6)]*. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

8.6 Renal Impairment

The efficacy and safety of JARDIANCE were evaluated in a study of patients with mild and moderate renal impairment *[see Clinical Studies (14.3)]*. In this study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 m^2, 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 m^2 and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose lowering benefit of JARDIANCE 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (5.3)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

The efficacy and safety of JARDIANCE have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. JARDIANCE is not expected to be effective in these patient populations *[see Dosage and Administration (2.2), Contraindications (4) and Warnings and Precautions (5.1, 5.3)]*.

8.7 Hepatic Impairment

JARDIANCE may be used in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

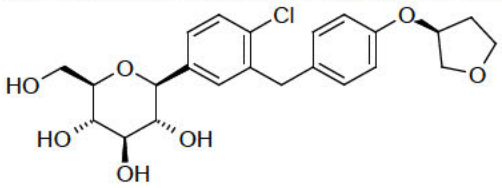
In the event of an overdose with JARDIANCE, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied.

11 DESCRIPTION

JARDIANCE tablets contain empagliflozin, an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2).

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).

Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

Each film-coated tablet of JARDIANCE contains 10 mg or 25 mg of empagliflozin (free base) and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, and yellow ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

12.2 Pharmacodynamics

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of JARDIANCE and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg JARDIANCE once daily *[see Clinical Studies (14)]*.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of JARDIANCE 25 mg, JARDIANCE 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution
The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism
No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Specific Populations
Renal Impairment
In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Hepatic Impairment
In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Effects of Age, Body Mass Index, Gender, and Race
Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin *[see Use in Specific Populations (8.5)]*.

Pediatric
Studies characterizing the pharmacokinetics of empagliflozin in pediatric patients have not been performed.

Drug Interactions

In vitro Assessment of Drug Interactions

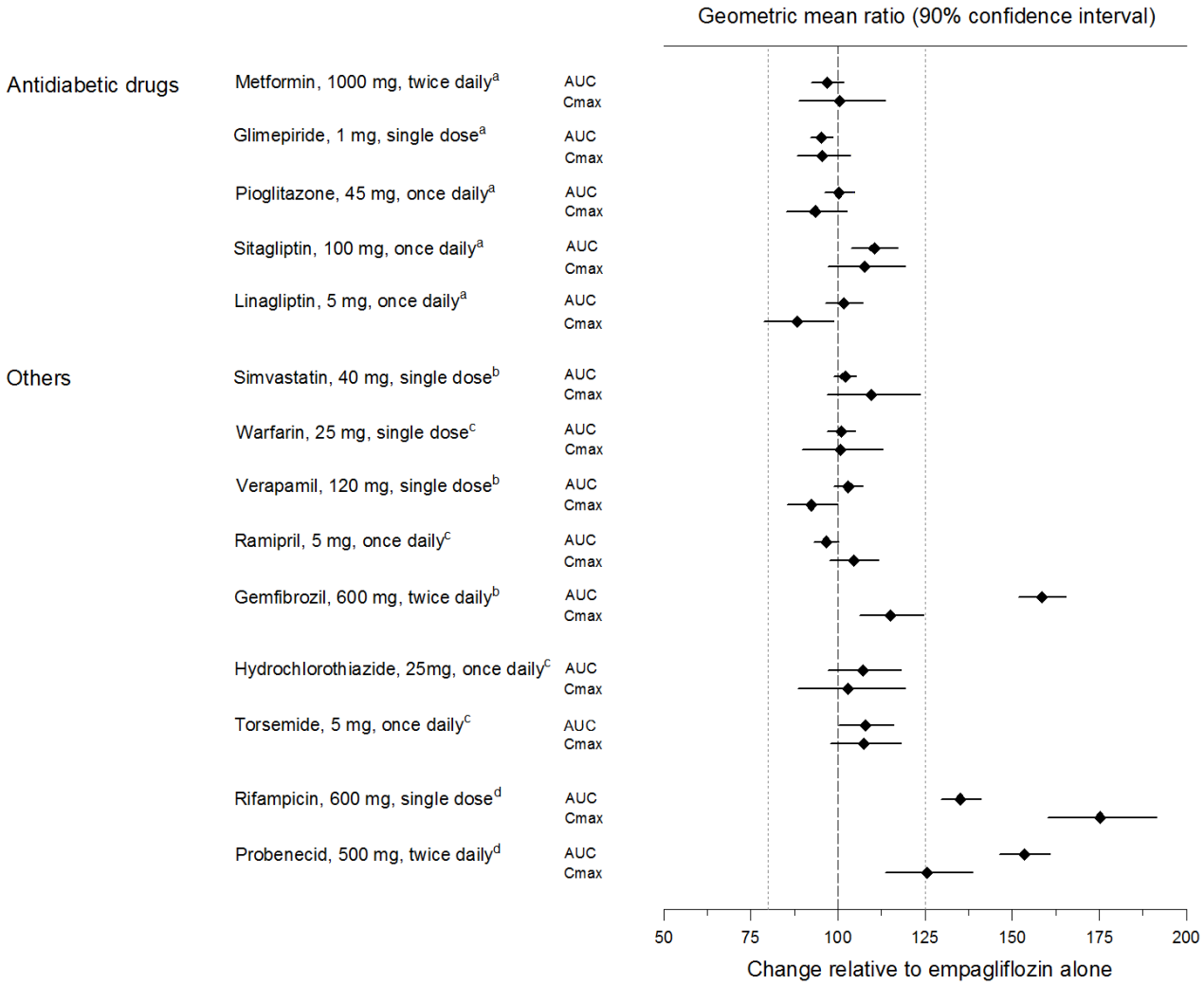
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

No dose adjustment of JARDIANCE is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, hydrochlorothiazide, and torsemide in healthy volunteers (see Figure 1). The observed increases in overall exposure (AUC) of empagliflozin following coadministration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

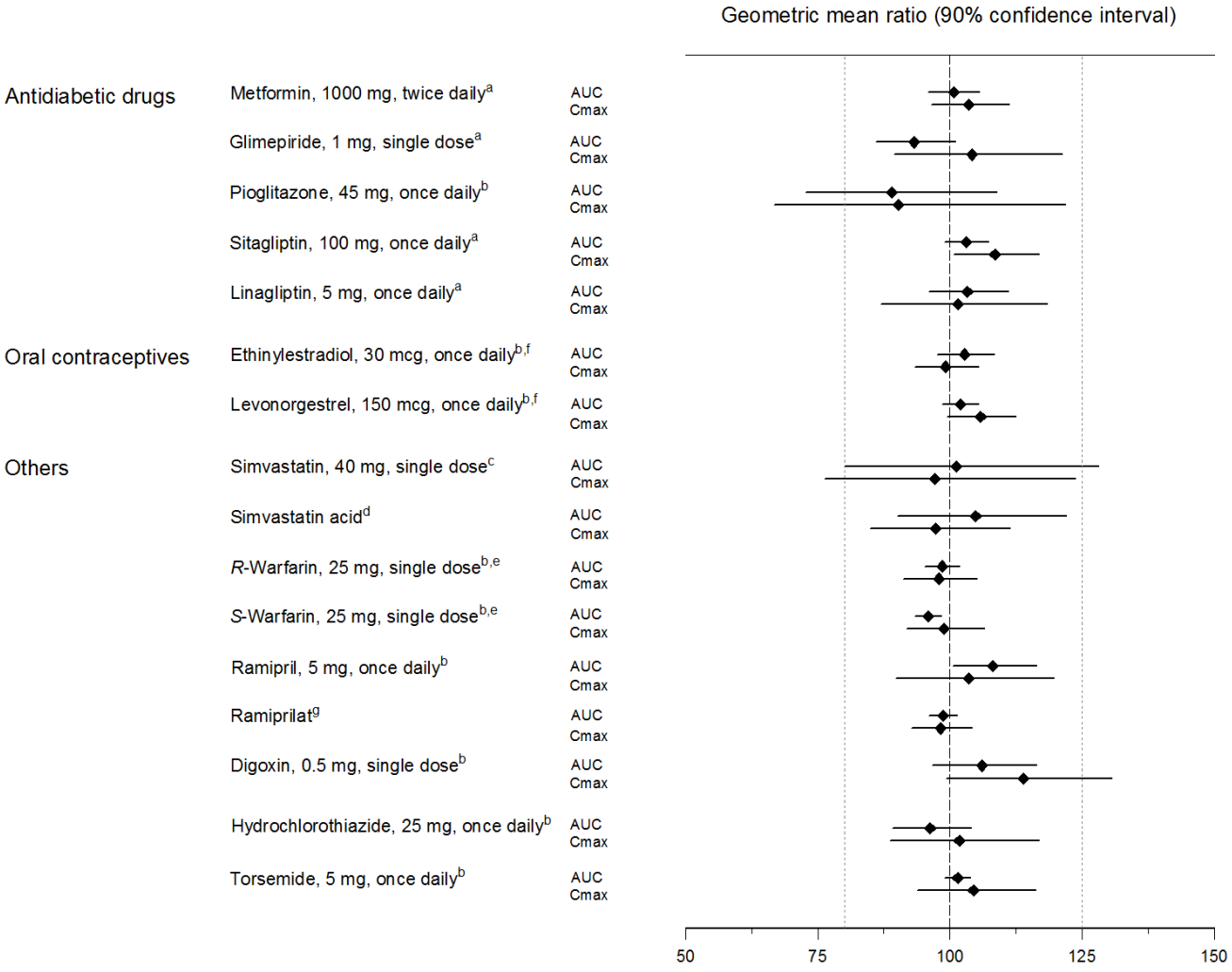
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, once daily; [c]empagliflozin, 25 mg, single dose; [d]administered as simvastatin; [e]administered as warfarin racemic mixture; [f]administered as Microgynon®; [g]administered as ramipril

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1000 mg/kg/day, which is approximately 45 times the exposure of the maximum

clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Mutagenesis
Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* L5178Y $tk^{+/-}$ mouse lymphoma cell assay, and an *in vivo* micronucleus assay in rats.

Impairment of Fertility
Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

14 CLINICAL STUDIES

JARDIANCE has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone, linagliptin, and insulin. JARDIANCE has also been studied in patients with type 2 diabetes with mild or moderate renal impairment.

In patients with type 2 diabetes, treatment with JARDIANCE reduced hemoglobin A1c (HbA1c), compared to placebo. The reduction in HbA1c for JARDIANCE compared with placebo was observed across subgroups including gender, race, geographic region, baseline BMI and duration of disease.

14.1 Monotherapy

A total of 986 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE monotherapy.

Treatment-naïve patients with inadequately controlled type 2 diabetes entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10% were randomized to placebo, JARDIANCE 10 mg, JARDIANCE 25 mg, or a reference comparator.

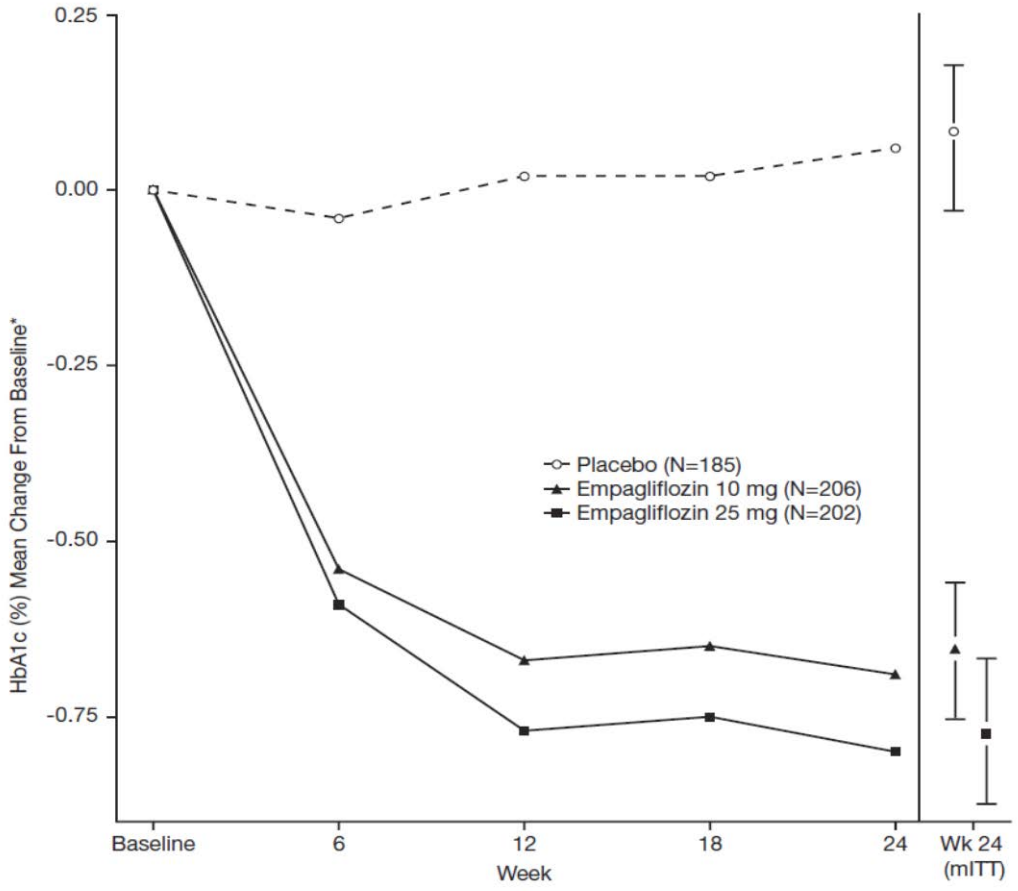
At Week 24, treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), fasting plasma glucose (FPG), and body weight compared with placebo (see Table 4 and Figure 3).

Table 4 Results at Week 24 From a Placebo-Controlled Monotherapy Study of JARDIANCE

	JARDIANCE 10 mg N=224	JARDIANCE 25 mg N=224	Placebo N=228
HbA1c (%)[a]			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-0.7[b] (-0.9, -0.6)	-0.9[b] (-1.0, -0.7)	--
Patients [n (%)] achieving HbA1c <7%	72 (35%)	88 (44%)	25 (12%)
FPG (mg/dL)[c]			
Baseline (mean)	153	153	155
Change from baseline (adjusted mean)	-19	-25	12
Difference from placebo (adjusted mean) (95% CI)	-31 (-37, -26)	-36 (-42, -31)	--
Body Weight			
Baseline (mean) in kg	78	78	78
% change from baseline (adjusted mean)	-2.8	-3.2	-0.4
Difference from placebo (adjusted mean) (95% CI)	-2.5[b] (-3.1, -1.9)	-2.8[b] (-3.4, -2.2)	--

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 9.4%, 9.4%, and 30.7% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.
[b]ANCOVA derived p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for JARDIANCE 10 mg, n=223, for JARDIANCE 25 mg, n=223, and for placebo, n=226

Figure 3 Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT Population) - LOCF



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, p-value=0.0231) in patients randomized to 10 mg of JARDIANCE and by -3.4 mmHg (placebo-corrected, p-value=0.0028) in patients randomized to 25 mg of JARDIANCE.

14.2 Combination Therapy

Add-On Combination Therapy with Metformin

A total of 637 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with metformin.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered an open-label 2 week placebo run-in. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10% were randomized to placebo, JARDIANCE 10 mg, or JARDIANCE 25 mg.

At Week 24, treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 5).

Table 5 Results at Week 24 From a Placebo-Controlled Study for JARDIANCE used in Combination with Metformin

	JARDIANCE 10 mg + Metformin N=217	**JARDIANCE 25 mg + Metformin N=213**	**Placebo + Metformin N=207**
HbA1c (%)[a]			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	-0.1
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6[b] (-0.7, -0.4)	-0.6[b] (-0.8, -0.5)	--
Patients [n (%)] achieving HbA1c <7%	75 (38%)	74 (39%)	23 (13%)
FPG (mg/dL)[c]			
Baseline (mean)	155	149	156
Change from baseline (adjusted mean)	-20	-22	6
Difference from placebo + metformin (adjusted mean)	-26	-29	--
Body Weight			
Baseline mean in kg	82	82	80
% change from baseline (adjusted mean)	-2.5	-2.9	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.0[b] (-2.6, -1.4)	-2.5[b] (-3.1, -1.9)	--

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 9.7%, 14.1%, and 24.6% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

[c]FPG (mg/dL); for JARDIANCE 10 mg, n=216, for JARDIANCE 25 mg, n=213, and for placebo, n=207

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-corrected, p-value <0.0001) for JARDIANCE 10 mg and -4.8 mmHg (placebo-corrected, p-value <0.0001) for JARDIANCE 25 mg.

Initial Combination Therapy with Metformin
A total of 1364 patients with type 2 diabetes participated in a double-blind, randomized, active-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with metformin as initial therapy compared to the corresponding individual components.

Treatment-naïve patients with inadequately controlled type 2 diabetes entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10.5% were randomized to one of 8 active-treatment arms: JARDIANCE 10 mg or 25 mg; metformin 1000 mg, or 2000 mg; JARDIANCE 10 mg in combination with 1000 mg or 2000 mg metformin; or JARDIANCE 25 mg in combination with 1000 mg or 2000 mg metformin.

At Week 24, initial therapy of JARDIANCE in combination with metformin provided statistically significant reductions in HbA1c (p-value <0.01) compared to the individual components (see Table 6).

Table 6 Glycemic Parameters at 24 Weeks in a Study Comparing JARDIANCE and Metformin to the Individual Components as Initial Therapy

	JARDIANCE 10 mg + Metformin 1000 mg[a] N=161	**JARDIANCE 10 mg + Metformin 2000 mg[a] N=167**	**JARDIANCE 25 mg + Metformin 1000 mg[a] N=165**	**JARDIANCE 25 mg + Metformin 2000 mg[a] N=169**	**JARDIANCE 10 mg N=169**	**JARDIANCE 25 mg N=163**	**Metformin 1000 mg[a] N=167**	**Metformin 2000 mg[a] N=162**
HbA1c (%)								
Baseline (mean)	8.7	8.7	8.8	8.7	8.6	8.9	8.7	8.6
Change from baseline (adjusted mean)	-2.0	-2.1	-1.9	-2.1	-1.4	-1.4	-1.2	-1.8
Comparison vs JARDIANCE (adjusted mean) (95% CI)	-0.6[b] (-0.9, -0.4)	-0.7[b] (-1.0, -0.5)	-0.6[c] (-0.8, -0.3)	-0.7[c] (-1.0, -0.5)	--	--	--	--
Comparison vs metformin (adjusted mean) (95% CI)	-0.8[b] (-1.0, -0.6)	-0.3[b] (-0.6, -0.1)	-0.8[c] (-1.0, -0.5)	-0.3[c] (-0.6, -0.1)	--	--	--	--

[a]Metformin total daily dose, administered in two equally divided doses per day.
[b]p-value ≤0.0062 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).
[c]p-value ≤0.0056 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

Add-On Combination Therapy with Metformin and Sulfonylurea
A total of 666 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with metformin plus a sulfonylurea.

Patients with inadequately controlled type 2 diabetes on at least 1500 mg per day of metformin and on a sulfonylurea, entered a 2 week open-label placebo run-in. At the end of the run-in, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, JARDIANCE 10 mg, or JARDIANCE 25 mg.

Treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 7).

Table 7 Results at Week 24 from a Placebo-Controlled Study for JARDIANCE in Combination with Metformin and Sulfonylurea

	JARDIANCE 10 mg + Metformin + SU N=225	JARDIANCE 25 mg + Metformin + SU N=216	Placebo + Metformin + SU N=225
HbA1c (%)[a]			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean)	-0.8	-0.8	-0.2
Difference from placebo (adjusted mean) (95% CI)	-0.6[b] (-0.8, -0.5)	-0.6[b] (-0.7, -0.4)	--
Patients [n (%)] achieving HbA1c <7%	55 (26%)	65 (32%)	20 (9%)
FPG (mg/dL)[c]			
Baseline (mean)	151	156	152
Change from baseline (adjusted mean)	-23	-23	6
Difference from placebo (adjusted mean)	-29	-29	--
Body Weight			
Baseline mean in kg	77	78	76
% change from baseline (adjusted mean)	-2.9	-3.2	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.4[b] (-3.0, -1.8)	-2.7[b] (-3.3, -2.1)	--

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 17.8%, 16.7%, and 25.3% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for JARDIANCE 10 mg, n=225, for JARDIANCE 25 mg, n=215, for placebo, n=224

In Combination with Linagliptin as Add-On to Metformin Therapy
A total of 686 patients with type 2 diabetes participated in a double-blind, active-controlled study to evaluate the efficacy and safety of JARDIANCE 10 mg or 25 mg in combination with linagliptin 5 mg compared to the individual components.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered a single-blind placebo run-in period for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10.5% were randomized 1:1:1:1:1 to one of 5 active-treatment arms of JARDIANCE 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg JARDIANCE as a fixed dose combination tablet.

At Week 24, JARDIANCE 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin. Treatment with JARDIANCE/linagliptin 25 mg/5 mg or JARDIANCE/linagliptin 10 mg/5 mg daily also resulted in a statistically significant reduction in body weight compared to linagliptin 5 mg (p-value <0.0001). There was no statistically significant difference in body weight compared to JARDIANCE alone.

Active-Controlled Study versus Glimepiride in Combination with Metformin
The efficacy of JARDIANCE was evaluated in a double-blind, glimepiride-controlled, study in 1545 patients with type 2 diabetes with insufficient glycemic control despite metformin therapy.

Patients with inadequate glycemic control and an HbA1c between 7% and 10% after a 2-week run-in period were randomized to glimepiride or JARDIANCE 25 mg.

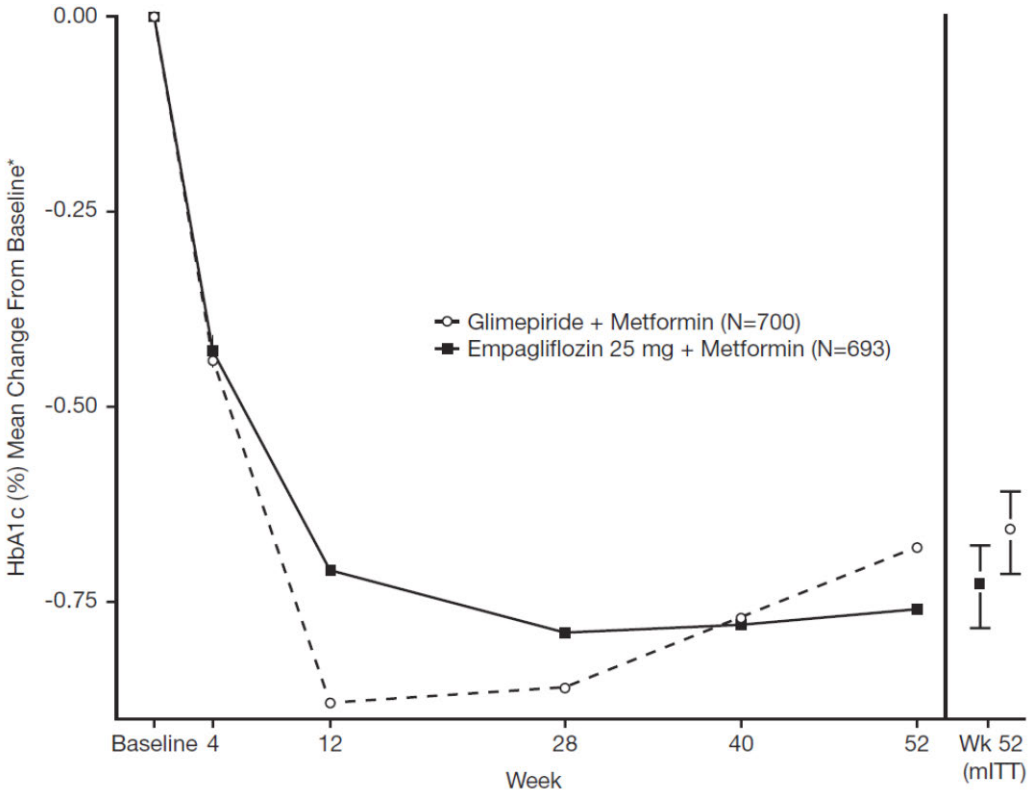
At Week 52, JARDIANCE 25 mg and glimepiride lowered HbA1c and FPG (see Table 8, Figure 4). The difference in observed effect size between JARDIANCE 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day.

Table 8 Results at Week 52 from an Active-Controlled Study Comparing JARDIANCE to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

	JARDIANCE 25 mg + Metformin N=765	**Glimepiride + Metformin N=780**
HbA1c (%)[a]		
Baseline (mean)	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.7
Difference from glimepiride (adjusted mean) (97.5% CI)	-0.07[b] (-0.15, 0.01)	--
FPG (mg/dL)[d]		
Baseline (mean)	150	150
Change from baseline (adjusted mean)	-19	-9
Difference from glimepiride (adjusted mean)	-11	--
Body Weight		
Baseline mean in kg	82.5	83
% change from baseline (adjusted mean)	-3.9	2.0
Difference from glimepiride (adjusted mean) (95% CI)	-5.9[c] (-6.3, -5.5)	--

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute data missing at Week 52. At Week 52, data was imputed for 15.3% and 21.9% of patients randomized to JARDIANCE 25 mg and glimepiride, respectively.
[b]Non-inferior, ANCOVA model p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region)
[c]ANCOVA p-value <0.0001 (Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[d]FPG (mg/dL); for JARDIANCE 25 mg, n=764, for placebo, n=779

Figure 4 Adjusted mean HbA1c Change at Each Time Point (Completers) and at Week 52 (mITT Population) - LOCF



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

At Week 52, the adjusted mean change from baseline in systolic blood pressure was -3.6 mmHg, compared to 2.2 mmHg for glimepiride. The differences between treatment groups for systolic blood pressure was statistically significant (p-value <0.0001).

At Week 104, the adjusted mean change from baseline in HbA1c was -0.75% for JARDIANCE 25 mg and -0.66% for glimepiride. The adjusted mean treatment difference was -0.09% with a 97.5% confidence interval of (-0.32%, 0.15%), excluding the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day. The Week 104 analysis included data with and without concomitant glycemic rescue medication, as well as off-treatment data. Missing data for patients not providing any information at the visit were imputed based on the observed off-treatment data. In this multiple imputation analysis, 13.9% of the data were imputed for JARDIANCE 25 mg and 12.9% for glimepiride.

At Week 104, JARDIANCE 25 mg daily resulted in a statistically significant difference in change from baseline for body weight compared to glimepiride (-3.1 kg for JARDIANCE 25 mg vs. +1.3 kg for glimepiride; ANCOVA-LOCF, p-value <0.0001).

Add-On Combination Therapy with Pioglitazone with or without Metformin
A total of 498 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with pioglitazone, with or without metformin.

Patients with inadequately controlled type 2 diabetes on metformin at a dose of at least 1500 mg per day and pioglitazone at a dose of at least 30 mg per day were placed into an open-label placebo run-in for 2 weeks. Patients with inadequate glycemic control and an HbA1c between 7% and 10% after the run-in period were randomized to placebo, JARDIANCE 10 mg, or JARDIANCE 25 mg.

Treatment with JARDIANCE 10 mg or 25 mg daily resulted in statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 9).

Table 9 Results of Placebo-Controlled Study for JARDIANCE in Combination Therapy with Pioglitazone

	JARDIANCE 10 mg + Pioglitazone N=165	**JARDIANCE 25 mg + Pioglitazone N=168**	**Placebo + Pioglitazone N=165**
HbA1c (%)[a]			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean)	-0.6	-0.7	-0.1
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-0.5[b] (-0.7, -0.3)	-0.6[b] (-0.8, -0.4)	--
Patients [n (%)] achieving HbA1c <7%	36 (24%)	48 (30%)	12 (8%)
FPG (mg/dL)[c]			
Baseline (mean)	152	152	152
Change from baseline (adjusted mean)	-17	-22	7
Difference from placebo + pioglitazone (adjusted mean) (97.5% CI)	-23[b] (-31.8, -15.2)	-28[b] (-36.7, -20.2)	--
Body Weight			
Baseline mean in kg	78	79	78
% change from baseline (adjusted mean)	-2.0	-1.8	0.6
Difference from placebo (adjusted mean) (95% CI)	-2.6[b] (-3.4, -1.8)	-2.4[b] (-3.2, -1.6)	--

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 10.9%, 8.3%, and 20.6% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and background medication. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for JARDIANCE 10 mg, n=163

Add-On Combination with Insulin with or without Metformin and/or Sulfonylureas
A total of 494 patients with type 2 diabetes inadequately controlled on insulin, or insulin in combination with oral drugs participated in a double-blind, placebo-controlled study to evaluate the efficacy of JARDIANCE as add-on therapy to insulin over 78 weeks.

Patients entered a 2-week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or sulfonylurea background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of JARDIANCE 10 mg, JARDIANCE 25 mg, or placebo. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 18 weeks of treatment. For the remaining 60 weeks, insulin could be adjusted. The mean total daily insulin dose at baseline for JARDIANCE 10 mg, 25 mg, and placebo was 45 IU, 48 IU, and 48 IU, respectively.

JARDIANCE used in combination with insulin (with or without metformin and/or sulfonylurea) provided statistically significant reductions in HbA1c and FPG compared to placebo after both 18 and 78 weeks of treatment (see Table 10). JARDIANCE 10 mg or 25 mg daily also resulted in statistically significantly greater percent body weight reduction compared to placebo.

Table 10 Results at Week 18 and 78 for a Placebo-Controlled Study for JARDIANCE in Combination with Insulin

	18 weeks (no insulin adjustment)			78 weeks (adjustable insulin dose after 18 weeks)		
	JARDIANCE 10 mg + Insulin N=169	**JARDIANCE 25 mg + Insulin N=155**	**Placebo + Insulin N=170**	**JARDIANCE 10 mg + Insulin N=169**	**JARDIANCE 25 mg + Insulin N=155**	**Placebo + Insulin N=170**
HbA1c (%)[a]						
Baseline (mean)	8.3	8.3	8.2	8.3	8.3	8.2
Change from baseline (adjusted mean)	-0.6	-0.7	0	-0.4	-0.6	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-0.6[b] (-0.8, -0.4)	-0.7[b] (-0.9, -0.5)	--	-0.5[b] (-0.7, -0.3)	-0.7[b] (-0.9, -0.5)	--
Patients (%) achieving HbA1c <7%	18.0	19.5	5.5	12.0	17.5	6.7
FPG (mg/dL)						
Baseline (mean)	138	146	142	138	146	142
Change from baseline (adjusted mean, SE)	-17.9 (3.2)	-19.1 (3.3)	10.4 (3.1)	-10.1 (3.2)	-15.2 (3.4)	2.8 (3.2)
Difference from placebo (adjusted mean) (95% CI)	-28.2[b] (-37.0, -19.5)	-29.5[b] (-38.4, -20.6)	--	-12.9[c] (-21.9, 3.9)	-17.9[b] (-27.0, -8.8)	--
Body Weight						
Baseline mean in kg	92	95	90	92	95	90
% change from baseline (adjusted mean)	-1.8	-1.4	-0.1	-2.4	-2.4	0.7
Difference from placebo (adjusted mean) (95% CI)	-1.7[d] (-3.0, -0.5)	-1.3[e] (-2.5, -0.0)	--	-3.0[b] (-4.4, -1.7)	-3.0[b] (-4.4, -1.6)	--

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 18 and 78. At Week 18, 21.3%, 30.3%, and 21.8% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively. At Week 78, 32.5%, 38.1% and 42.4% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, and region; FPG: MMRM model includes baseline FPG, baseline HbA1c, treatment, region, visit and visit by treatment interaction. Body weight: MMRM model includes baseline body weight, baseline HbA1c, treatment, region, visit and visit by treatment interaction.

[c]p-value=0.0049

[d]p-value=0.0052

[e]p-value=0.0463

Add-on Combination with MDI Insulin with or without Metformin
A total of 563 patients with type 2 diabetes inadequately controlled on multiple daily injections (MDI) of insulin (total daily dose >60 IU), alone or in combination with metformin, participated in a double-blind, placebo-controlled study to evaluate the efficacy of JARDIANCE as add-on therapy to MDI insulin over 18 weeks.

Patients entered a 2-week placebo run-in period on MDI insulin with or without metformin background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of JARDIANCE 10 mg, JARDIANCE 25 mg, or placebo. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 18 weeks of treatment. The mean total daily insulin dose at baseline for JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo was 88.6 IU, 90.4 IU, and 89.9 IU, respectively.

JARDIANCE 10 mg or 25 mg daily used in combination with MDI insulin (with or without metformin) provided statistically significant reductions in HbA1c compared to placebo after 18 weeks of treatment (see Table 11).

Table 11 Results at Week 18 for a Placebo-Controlled Study for JARDIANCE in Combination with Insulin and with or without Metformin

	JARDIANCE 10 mg + Insulin +/- Metformin N=186	**JARDIANCE 25 mg + Insulin +/- Metformin N=189**	**Placebo + Insulin +/- Metformin N=188**
HbA1c (%)[a]			
Baseline (mean)	8.4	8.3	8.3
Change from baseline (adjusted mean)	-0.9	-1.0	-0.5
Difference from placebo (adjusted mean) (95% CI)	-0.4[b] (-0.6, -0.3)	-0.5[b] (-0.7, -0.4)	--

[a]Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 18. At Week 18, 23.7%, 22.8% and 23.4% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, geographical region, and background medication).

During an extension period with treatment for up to 52 weeks, insulin could be adjusted to achieve defined glucose target levels. The change from baseline in HbA1c was maintained from 18 to 52 weeks with both JARDIANCE 10 mg and 25 mg. After 52 weeks, JARDIANCE 10 mg or 25 mg daily resulted in statistically greater percent body weight reduction compared to placebo (p-value <0.0001). The mean change in body weight from baseline was -1.95 kg for JARDIANCE 10 mg, and -2.04 kg for JARDIANCE 25 mg.

14.3 Renal Impairment
A total of 738 patients with type 2 diabetes and a baseline eGFR less than 90 mL/min/1.73 m^2 participated in a randomized, double-blind, placebo-controlled, parallel-group to evaluate the efficacy and safety of JARDIANCE in patients with type 2 diabetes and renal impairment. The trial population comprised of 290 patients with mild renal impairment (eGFR 60 to less than 90 mL/min/1.73 m^2), 374 patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and 74 with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2). A total of 194 patients with moderate renal impairment had a baseline eGFR of 30 to less than 45 mL/min/1.73 m^2 and 180 patients a baseline eGFR of 45 to less than 60 mL/min/1.73 m^2.

At Week 24, JARDIANCE 25 mg provided statistically significant reduction in HbA1c relative to placebo in patients with mild to moderate renal impairment (see Table 12). A statistically significant reduction relative to

placebo was also observed with JARDIANCE 25 mg in patients with either mild [-0.7 (95% CI: -0.9, -0.5)] or moderate [-0.4 (95% CI: -0.6, -0.3)] renal impairment and with JARDIANCE 10 mg in patients with mild [-0.5 (95% CI: -0.7, -0.3)] renal impairment.

The glucose lowering efficacy of JARDIANCE 25 mg decreased with decreasing level of renal function in the mild to moderate range. Least square mean Hb1Ac changes at 24 weeks were -0.6%, -0.5%, and -0.2% for those with a baseline eGFR of 60 to less than 90 mL/min/1.73 m^2, 45 to less than 60 mL/min/1.73 m^2, and 30 to less than 45 mL/min/1.73 m^2, respectively *[see Dosage and Administration (2) and Use in Specific Populations (8.6)]*. For placebo, least square mean HbA1c changes at 24 weeks were 0.1%, -0.1%, and 0.2% for patients with a baseline eGFR of 60 to less than 90 mL/min/1.73 m^2, 45 to less than 60 mL/min/1.73 m^2, and 30 to less than 45 mL/min/1.73 m^2, respectively.

Table 12 Results at Week 24 (LOCF) of Placebo-Controlled Study for JARDIANCE in Patients with Type 2 Diabetes and Renal Impairment

	Mild and Moderate Impairment[b]
	JARDIANCE 25 mg
HbA1c	
Number of patients	n=284
Comparison vs placebo (adjusted mean) (95% CI)	-0.5[a] (-0.6, -0.4)

[a]p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and background medication)
[b]eGFR 30 to less than 90 mL/min/1.73 m^2- Modified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 24.6% and 26.2% was imputed for patients randomized to JARDIANCE 25 mg and placebo, respectively.

For patients with severe renal impairment, the analyses of changes in HbA1c and FPG showed no discernible treatment effect of JARDIANCE 25 mg compared to placebo *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

JARDIANCE tablets are available in 10 mg and 25 mg strengths as follows:

10 mg tablets: pale yellow, round, biconvex and bevel-edged, film-coated tablets debossed with “S 10” on one side and the Boehringer Ingelheim company symbol on the other side.
Bottles of 30 (NDC 0597-0152-30)
Bottles of 90 (NDC 0597-0152-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0152-37), institutional pack.

25 mg tablets: pale yellow, oval, biconvex film-coated tablets, debossed with “S 25” on one side and the Boehringer Ingelheim company symbol on the other side.
Bottles of 30 (NDC 0597-0153-30)
Bottles of 90 (NDC 0597-0153-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0153-37), institutional pack.

Dispense in a well-closed container as defined in the USP.

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Instructions
Instruct patients to read the Patient Information before starting JARDIANCE therapy and to reread it each time the prescription is renewed. Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Inform patients of the potential risks and benefits of JARDIANCE and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take JARDIANCE only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

Inform patients that the most common adverse reactions associated with the use of JARDIANCE are urinary tract infections and mycotic genital infections.

Inform female patients of child bearing age that the use of JARDIANCE during pregnancy has not been studied in humans, and that JARDIANCE should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal data, JARDIANCE may cause fetal harm in the second and third trimesters. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue JARDIANCE or nursing, taking into account the importance of the drug to the mother. It is not known if JARDIANCE is excreted in breast milk; however, based on animal data, JARDIANCE may cause harm to nursing infants.

Hypotension
Inform patients that hypotension may occur with JARDIANCE and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.1)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis
Inform patients that ketoacidosis has been reported during use of JARDIANCE. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue JARDIANCE and seek medical advice immediately *[see Warnings and Precautions (5.2)]*.

Serious Urinary Tract Infections
Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.4)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)
Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.6)]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)
Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.6)]*.

Laboratory Tests
Inform patients that renal function should be assessed prior to initiation of JARDIANCE and monitored periodically thereafter.

Inform patients that elevated glucose in urinalysis is expected when taking JARDIANCE.

Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels toward the normal range. Hemoglobin A1c monitoring is especially useful for evaluating long-term glycemic control.

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PATIENT INFORMATION
JARDIANCE® (jar DEE ans)
(empagliflozin)
Tablets

What is the most important information I should know about JARDIANCE?

JARDIANCE can cause serious side effects, including:

- **Dehydration.** JARDIANCE can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension).

  You may be at higher risk of dehydration if you:
  - have low blood pressure
  - take medicines to lower your blood pressure, including diuretics (water pill)
  - are on low sodium (salt) diet
  - have kidney problems
  - are 65 years of age or older
- **Vaginal yeast infection.** Women who take JARDIANCE may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the penis (balanitis or balanoposthitis).** Men who take JARDIANCE may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - rash of the penis
  - foul smelling discharge from the penis
  - pain in the skin around penis

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

What is JARDIANCE?

- JARDIANCE is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- JARDIANCE is not for people with type 1 diabetes.
- JARDIANCE is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- It is not known if JARDIANCE is safe and effective in children under 18 years of age.

Who should not take JARDIANCE?

Do not take JARDIANCE if you:

- are allergic to empagliflozin or any of the ingredients in JARDIANCE. See the end of this leaflet for a list of ingredients in JARDIANCE.
- have severe kidney problems or are on dialysis

What should I tell my doctor before using JARDIANCE?

Before you take JARDIANCE, tell your doctor if you:

- have kidney problems
- have liver problems
- have a history of urinary tract infections or problems with urination
- are going to have surgery
- are eating less due to illness, surgery, or a change in your diet
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas
- drink alcohol very often, or drink a lot of alcohol in the short term (“binge” drinking)
- have any other medical conditions
- are pregnant or planning to become pregnant. It is not known if JARDIANCE will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if JARDIANCE passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take JARDIANCE.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines,

vitamins, and herbal supplements.

JARDIANCE may affect the way other medicines work, and other medicines may affect how JARDIANCE works.

Especially tell your doctor if you take:
- diuretics (water pills)
- insulin or other medicines that can lower your blood sugar

Ask your doctor or pharmacist for a list of these medicines if you are not sure if your medicine is listed above.

How should I take JARDIANCE?

- Take JARDIANCE exactly as your doctor tells you to take it.
- Take JARDIANCE by mouth 1 time in the morning each day, with or without food.
- Your doctor may change your dose if needed.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of JARDIANCE at the same time. Talk with your doctor if you have questions about a missed dose.
- Your doctor may tell you to take JARDIANCE along with other diabetes medicines. Low blood sugar can happen more often when JARDIANCE is taken with certain other diabetes medicines. See **"What are the possible side effects of JARDIANCE?"**
- If you take too much JARDIANCE, call your doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JARDIANCE.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin HbA1c.
- When taking JARDIANCE, you may have sugar in your urine, which will show up on a urine test.

What are the possible side effects of JARDIANCE?

JARDIANCE may cause serious side effects, including:
- See "**What is the most important information I should know about JARDIANCE?**"
- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes or type 2 diabetes,** during treatment with JARDIANCE. Ketoacidosis can be life-threatening and may need to be treated in a hospital. **Ketoacidosis can happen with JARDIANCE even if your blood sugar is less than 250 mg/dL. Stop taking JARDIANCE and call your doctor right away if you get any of the following symptoms**:
  - o nausea
  - o vomiting
  - o stomach-area (abdominal) pain
  - o tiredness
  - o trouble breathing

  If you get any of these symptoms during treatment with JARDIANCE, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
- **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking JARDIANCE. Tell your doctor if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.
- **Low blood sugar (hypoglycemia).** If you take JARDIANCE with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take JARDIANCE. Signs and symptoms of low blood sugar may include:
  - o headache
  - o drowsiness
  - o weakness
  - o irritability
  - o hunger
  - o fast heartbeat
  - o confusion
  - o shaking or feeling jittery
  - o dizziness
  - o sweating
- **Kidney problems,** especially in people 75 years of age or older and people who already have kidney problems
- **Increased fats in your blood (cholesterol)**

These are not all the possible side effects of JARDIANCE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JARDIANCE?

Store JARDIANCE at room temperature 68°F to 77°F (20°C to 25°C).

General information about the safe and effective use of JARDIANCE.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information. Do not use JARDIANCE for a condition for which it is not prescribed. Do not give JARDIANCE to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about JARDIANCE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about JARDIANCE that is written for health professionals.

For more information about JARDIANCE, go to www.jardiance.com, scan the code below, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in JARDIANCE?

Active Ingredient: empagliflozin

Inactive Ingredients: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, and yellow ferric oxide.

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc.; Ridgefield, CT 06877 USA
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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: March 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s005

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(see electronic signature)
From	William H Chong, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA-204629, Suppl. 5 NDA-206111, Suppl. 1
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	NDA-204629: May 20, 2015 NDA-206111: September 11, 2015
PDUFA Goal Date	NDA-204629: March 20, 2016 NDA-206111: July 11, 2016
Proprietary Name / Established (USAN) names	NDA-204629: JARDIANCE (empagliflozin) NDA-206111: SYNJARDY (empagliflozin and metformin hydrochloride)
Dosage forms / Strength	NDA-204629: 10 mg and 25 mg tablets NDA-206111: 5 mg/500 mg, 5 mg/1000 mg, 12.5 mg/500 mg, 12.5 mg/1000 mg (empagliflozin/metformin) tablets
Proposed Indication(s)	NDA-204629: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. NDA-206111: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate
Recommendation:	*NDA-204629, Suppl-5: Approval pending agreement on labeling language* *NDA-206111, Suppl-1: Approval pending agreement on labeling language*

1. Introduction

JARDIANCE (empagliflozin) and SYNJARDY (empagliflozin and metformin hydrochloride) are approved drug products for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). In these supplements, Boehringer Ingelheim submitted the results of a clinical study designed to compare the efficacy of empagliflozin and metformin started concomitantly with the efficacy of the individual components.

2. Background

Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor approved on August 1, 2014 for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. By inhibiting glucose reabsorption in the kidney, empagliflozin increases the urinary excretion of glucose and thus reduces plasma glucose levels. Empagliflozin is marketed under the proprietary name JARDIANCE.

Metformin is a biguanide approved on March 3, 1995 for use as an adjunct to diet and exercise to improve glycemic control in adults and children with T2DM. By decreasing hepatic gluconeogenesis, and improving peripheral insulin sensitivity leading to increased peripheral glucose uptake and utilization, metformin lowers plasma glucose levels.

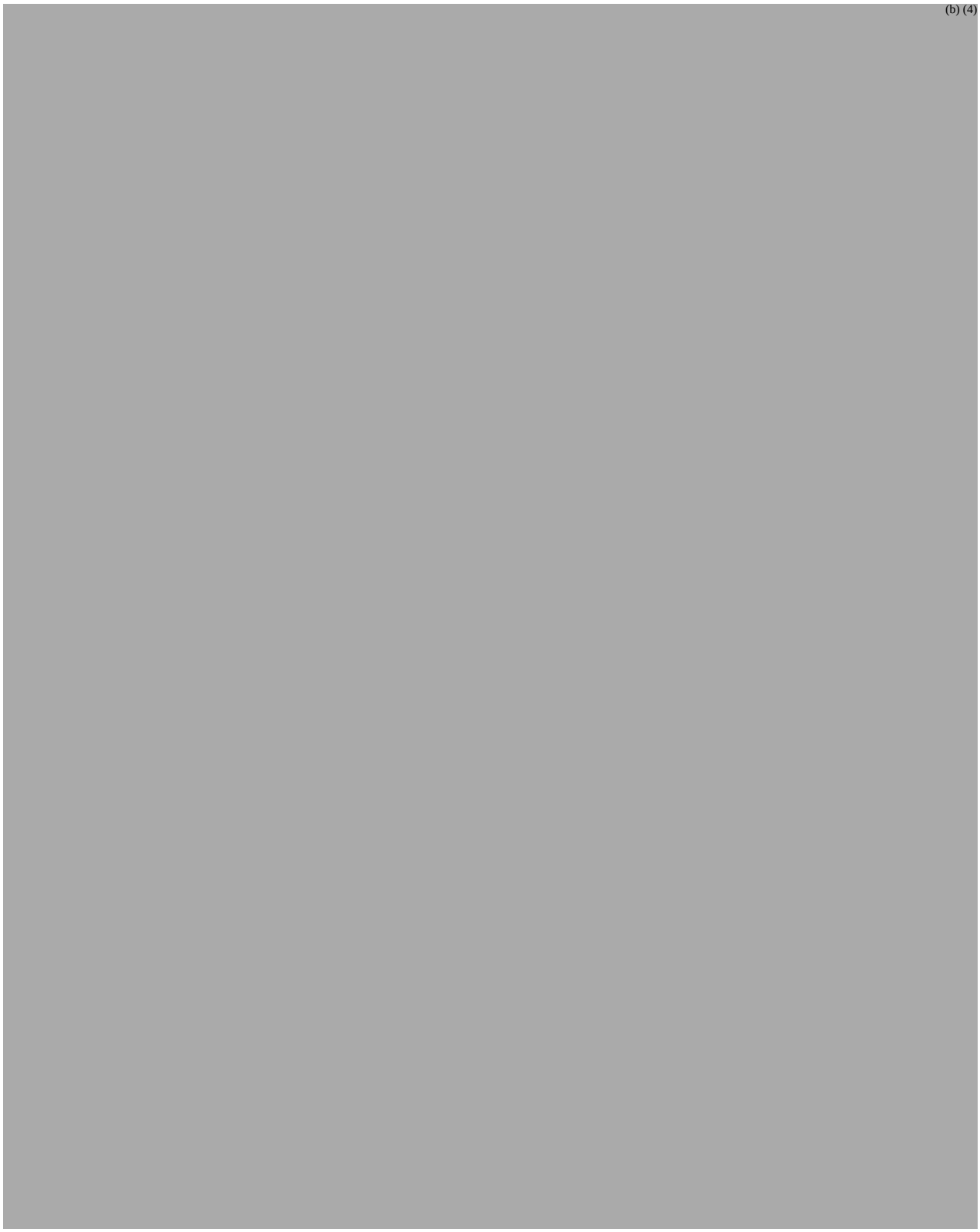
A fixed combination of empagliflozin and metformin hydrochloride was approved on August 26, 2015 for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin. This fixed combination drug product (FCDP) is marketed under the proprietary name SYNJARDY.

Boehringer Ingelheim (hereafter referred to as "the applicant") has submitted data from a single clinical study (study 1276.1) as supplements to NDA-204629 (JARDIANCE) and NDA-206111 (SYNJARDY). In this study, the applicant has studied the efficacy and safety of initial therapy with empagliflozin and metformin alone and in combination. Additional clinical pharmacology and nonclinical data were reviewed as part of these supplements as the applicant has proposed additional language in section 12.3 and (b) (4) of the labels.

3. CMC/Device

Not applicable. There are no CMC or device data in the submitted supplements.

4. Nonclinical Pharmacology/Toxicology



(b) (4)

5. Clinical Pharmacology/Biopharmaceutics

A Clinical Pharmacology review was completed by Dr. Suryanarayana Sista as part of this supplement. Included in the supplement is a report from an in vitro study evaluating the potential for inhibition of human UDP-glucuronosyltransferase enzymes by empagliflozin, and an assessment of drug interaction potential. Based on the findings from the in vitro study (see Table 1 and Table 2 of Dr. Sista's review, excerpted below), the applicant has concluded that empagliflozin does not inhibit UDP-glucuronosyltransferase enzymes and that the potential for drug-drug interaction between empagliflozin and concomitantly administered substrates of UGT1A3, UGT1A8, UGT1A9, and UG2B7 is remote. Subsequently, the applicant does not believe that in vivo studies are needed.

Dr. Sista agrees with these conclusions. Additionally, he has reviewed the proposed language in section 12.3 of the label and finds the language summarizing the findings from this study acceptable. I agree with his recommendation to accept the proposed language.

Table 1 Empagliflozin IC_{50} and K_i Values

UGT	IC_{50} [1] (μM)	K_i [2] (μM)
rUGT1A3	>100	>50
UGT1A3 (in HLM)	>100	>50
rUGT1A8	>>100	>>50
UGT1A9 (in HLM)	>100	>50
UGT2B7 (in HLM)	>>100	>>50
UGT2B7 (in HLM) with BSA	>>100	>>50

1. Experiments were conducted at two separate occasions; n=3 for each experiment
2. Competitive inhibition was assumed and K_i value was calculated as $IC_{50}/2$, since the concentration of substrate was equal to the apparent K_m value.

Table 2 Assessment of drug-drug interaction potential for empagliflozin

UGT	K_i (μM)	[a] $[I]_{gut}/K_i$	[b] C_{max}/K_i	[b,c] $C_{max,unbound}/K_i$	Potential for DDI
rUGT1A3	>50	<4.4	<0.014	<0.002	Remote
UGT 1A3 (in HLM)	>50	<4.4	<0.014	<0.002	Remote
rUGT1A8	>>50	<4.4	<0.014	<0.002	Remote
UGT 1A9 (in HLM)	>50	<4.4	<0.014	<0.002	Remote
UGT 2B7 (in HLM)	>>50	<4.4	<0.014	<0.002	Remote
UGT 2B7 (in HLM) with BSA[d]	>>50	<4.4	<0.014	<0.002	Remote

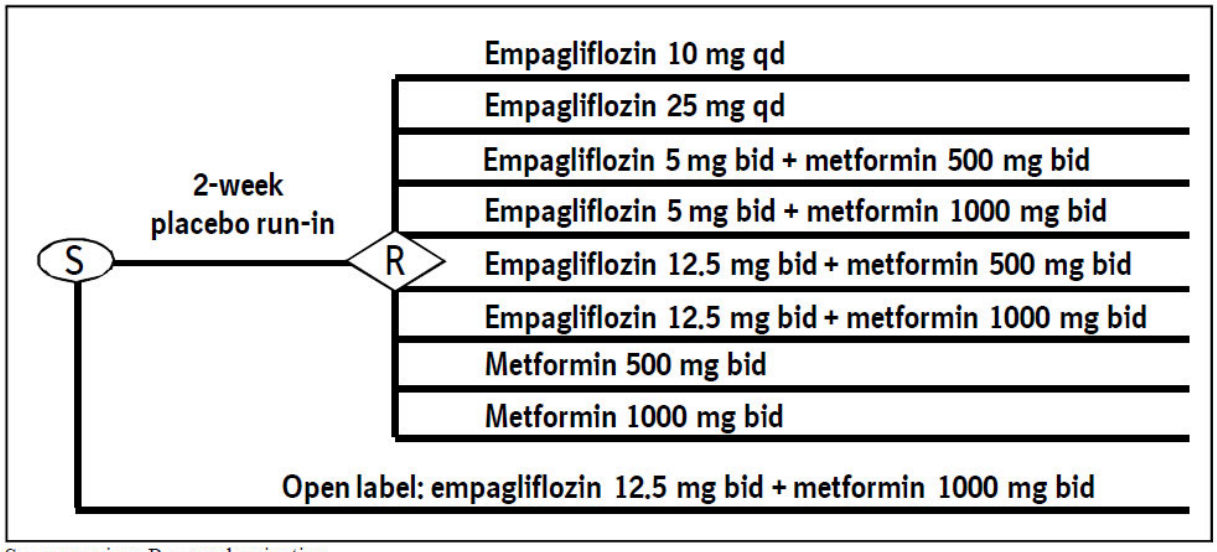
[a] EMA DDI criteria for an enzyme with marked abundance in enterocyte: an in-vivo DDI study is recommended if the $[I]_{gut}/K_i \geq 10$ where $[I]_{gut}$ is the maximum dose taken at one occasion/250 mL
[b] EMA DDI criteria for enzymes in the liver, or in organs, exposed to the drug through the systematic circulation: an in-vivo DDI study is recommended if the $[I]/K_i \geq 0.02$ where [I] is the unbound mean C_{max} obtained at the highest recommended dose. For completeness of the evaluation, the total C_{max} was also used for assessment.
[c] DDI was assessed using the unbound concentration (plasma protein binding=83.7%) [4]
[d] Assay was conducted in the presence of BSA (bovine serum albumin); other assays were conducted in the absence of BSA.

6. Clinical Microbiology

Not applicable. There are no clinical microbiology data in the submitted supplements.

7. Clinical/Statistical- Efficacy

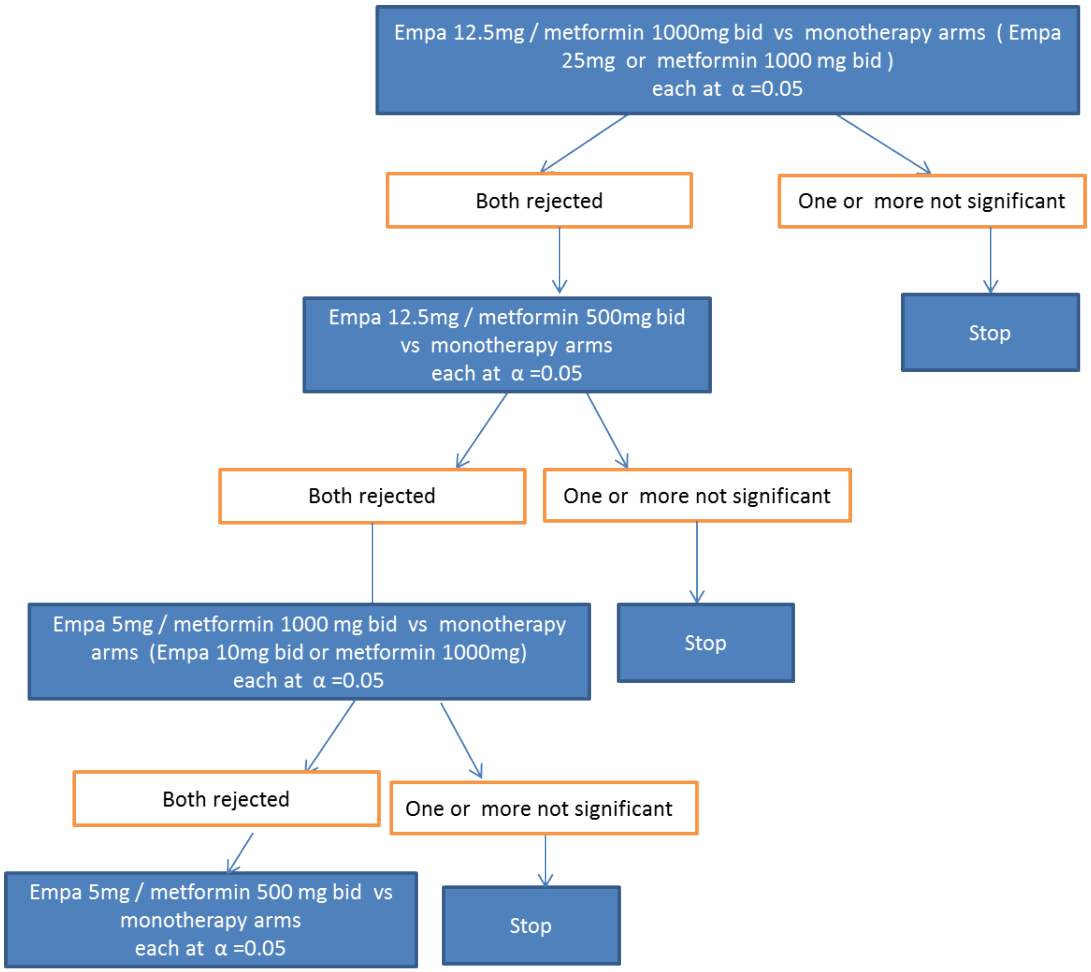
Study 1276.1 (entitled "A 24-week phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug-naïve patients with type 2 diabetes mellitus") was a factorial study designed to compare the efficacy of initiating dual therapy with empagliflozin and metformin to initiating either empagliflozin or metformin alone. To achieve this, the applicant used eight different treatment arms to span the range of possible dose combinations. An open label arm was also included for those subjects with HbA1c > 10% but that were otherwise eligible (see below).



S = screening, R = randomization
Source: Excerpted from Figure 3.1: 1 from v1.0 (dated April 30, 2012) of the study protocol

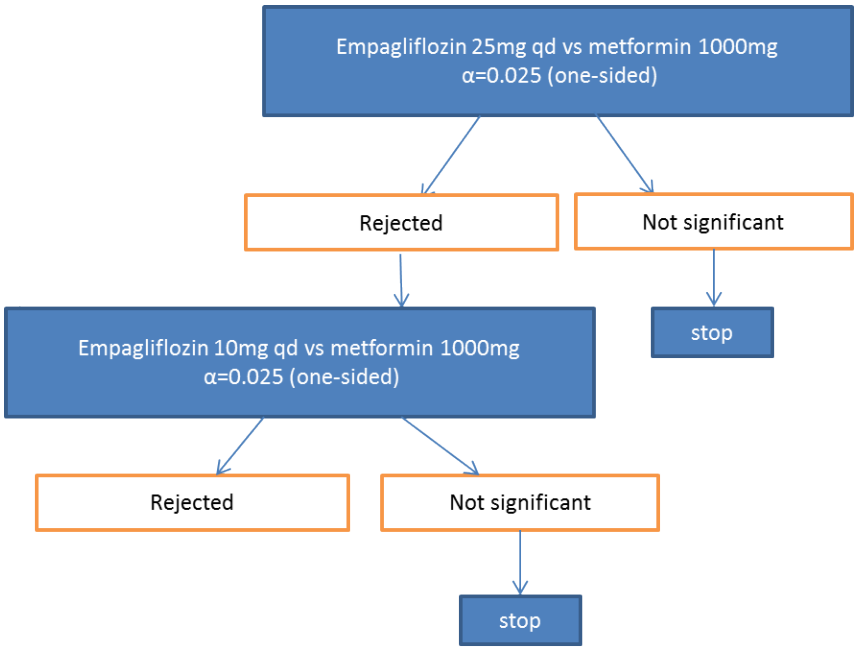
The hierarchical testing sequence outlined for this study included comparisons for superiority of combination therapy to the respective doses of the individual drugs. If superiority was demonstrated for all of the combination doses, then the statistical plan allowed for testing of non-inferiority of empagliflozin vs. metformin 1000 mg (see Figure 1 and Figure 2 below, excerpted from Dr. Sinks' Statistical Review).

Figure 1: Schematic of hierarchical testing sequence for superiority of combination compared to individual components



Source: Excerpted from Figure 1 of Dr. Sinks' Statistical Review

Figure 2: Schematic of hierarchical testing sequence for non-inferiority of empagliflozin compared to metformin 1000 mg twice daily



Source: Excerpted from Figure 2 of Dr. Sinks' Statistical Review

Two additional secondary endpoints were included in the statistical plan: change in fasting plasma glucose at 24 weeks and change in body weight at 24 weeks. The planned comparisons for the secondary endpoints were the combination therapy arm to the respective individual components.

Statistical issues identified in Dr. Sinks' review include the choice of analysis population and lack of data from subjects that prematurely discontinued study drug.

The applicant's pre-specified primary analysis population was the full analysis set (all randomized subjects treated with at least 1 dose of study drug and at least 1 on-treatment HbA1c measurement). The Statistical Review notes that though this was the pre-specified analysis population, the analysis presented by the applicant as the primary analysis included only the on-treatment subjects (i.e., completers [did not include data from subjects that prematurely discontinued therapy]). The overall amount of missing data was 10.2% (range of 6.5% to 12.3%; see Table 4 of Dr. Sinks' review [excerpted below]).

Table 4 Percentage of missingness by treatment group –Treated Set

Planned Treatment	n	Baseline	Week 6	Week 12	Week 18	Week 24
E10 QD	172	0.0%	2.9%	2.9%	5.8%	7.6%
E12.5+M1000 BID	170	0.0%	1.2%	4.7%	5.9%	6.5%
E12.5+M500 BID	170	0.0%	3.5%	8.2%	9.4%	11.8%
E25 QD	167	0.0%	3.6%	6.0%	10.8%	12.0%
E5+M1000BID	171	0.0%	2.9%	5.8%	7.0%	11.1%
E5+M500 BID	169	0.0%	5.9%	5.9%	7.7%	8.9%
M1000 BID	170	0.0%	4.7%	10.0%	10.0%	11.2%
M500 BID	171	0.0%	2.3%	7.6%	9.4%	12.3%

Source: Excerpted from Dr. Sinks' Statistical Review

As the analysis presented by the applicant only includes data from those patients that remained on treatment, it assumes that outcomes after treatment discontinuation are missing at random. Additional analyses were requested to include data from all randomized subjects regardless of treatment discontinuation, but the applicant reported that data was not collected for subjects that prematurely discontinued. The applicant provided additional analyses using varying approaches to imputing the missing data.

Dr. Sinks has utilized an additional imputation strategy for missing data and assumed that subjects who discontinued prematurely would no longer benefit and would return to baseline. Additionally, the population used included all randomized subjects who took at least 1 dose of study drug regardless of adherence.

Both approaches (i.e., the applicant's primary analysis and Dr. Sinks' analysis) demonstrated superiority of combination therapy over the individual components (see Table 11.1.1.1: 1 of the study report for study 1276.1 and Table 5 of Dr. Sinks' Statistical Review [both excerpted below]).

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Number of patients in analysis set	169	165	167	161	164	169	164	168
Baseline								
Mean baseline HbA_{1c} (SE)	8.66 (0.09)	8.84 (0.10)	8.65 (0.10)	8.68 (0.10)	8.86 (0.10)	8.62 (0.10)	8.55 (0.09)	8.69 (0.08)
Week 24								
Number of analysed patients	159	149	151	153	143	156	146	142
Mean HbA_{1c} (SE)	6.56 (0.08)	6.84 (0.09)	6.49 (0.08)	6.67 (0.07)	7.30 (0.09)	7.18 (0.09)	6.72 (0.08)	7.35 (0.11)
Change from baseline								
Mean (SE)	-2.12 (0.09)	-1.99 (0.11)	-2.12 (0.09)	-2.01 (0.09)	-1.48 (0.10)	-1.35 (0.09)	-1.81 (0.10)	-1.30 (0.09)
Adjusted[1] mean (SE)	-2.08 (0.08)	-1.93 (0.08)	-2.07 (0.08)	-1.98 (0.08)	-1.36 (0.08)	-1.35 (0.08)	-1.75 (0.09)	-1.18 (0.08)
Comparison vs. M1000 bid								
Adjusted[1] mean (SE)	-0.33 (0.12)	-	-0.33 (0.12)	-	0.39 (0.12)	0.40 (0.12)	-	-
95% CI	(-0.56, -0.10)	-	(-0.56, -0.09)	-	(0.15, 0.62)	(0.16, 0.63)	-	-
p-value non-inferiority[2]					0.6246	0.6558		
p-value superiority	0.0056	-	0.0062	-	-	-	-	-
Comparison vs. E25 qd								
Adjusted[1] mean (SE)	-0.72 (0.12)	-0.57 (0.12)	-	-	-	-	-	-
95% CI	(-0.95, -0.48)	(-0.81, -0.34)	-	-	-	-	-	-
p-value superiority	<0.0001	<0.0001	-	-	-	-	-	-
Comparison vs. M500 bid								
Adjusted[1] mean (SE)	-	-0.75 (0.12)	-	-0.79 (0.12)	-	-	-	-
95% CI	-	(-0.98, -0.51)	-	(-1.03, -0.56)	-	-	-	-
p-value superiority	-	<0.0001	-	<0.0001	-	-	-	-
Comparison vs. E10 qd								
Adjusted[1] mean (SE)	-	-	-0.72 (0.12)	-0.63 (0.12)	-	-	-	-
95% CI	-	-	(-0.95, -0.49)	(-0.86, -0.40)	-	-	-	-
p-value superiority	-	-	<0.0001	<0.0001	-	-	-	-

SE = standard error; CI = confidence interval

[1] The MMRM model includes baseline HbA_{1c} as linear covariate and baseline eGFR (MDRD), geographical region, treatment, visit, and visit-by-treatment interaction as fixed effects. The covariance used to fit the model was unstructured.
[2] One-sided test relative to a pre-specified margin of 0.35%

Source: Excerpted from Table 11.1.1.1: 1 of the study report for study 1276.1

Table 5 HbA1c (%) change from baseline ANOVA results at Week 24 –TS (OC-IR) (FDA's Results)

	LS Mean (SE)	Comparison vs E25 QD (95% CI) P-value	Comparison vs M1000 BID (95% CI) P-value	Comparison vs M500 BID (95% CI) P-value	Comparison vs E10 QD (95% CI) P-value
Combination					
E12.5+M1000 BID (n=170)	-1.77 (0.14)	-0.79 (-1.04, -0.54) <0.0001	-0.38 (-0.63, -0.13) <0.0001		
E12.5+M500 BID (n=170)	-1.44 (0.14)	-0.45 (-0.71, -0.20) 0.0004		-0.54 (-0.79, -0.29) <0.0001	
E5+M1000 BID (n=171)	-1.69 (0.14)		-0.30 (-0.55, -0.05) 0.0203		-0.63 (-0.88, -0.38) <0.0001
E5+M500 BID (n=169)	-1.60 (0.14)			-0.70 (-0.95, -0.45) <0.0001	-0.53 (-0.78, -0.29) <0.0001
	LS Mean (SE)		**Comparison vs M1000 BID (95% CI) P-value***		
Monotherapy					
E25 QD (n=167)	-0.99 (0.14)		0.41 (0.16, 0.66) 0.6471		
E10 QD (n=172)	-1.06 (0.14)		0.33 (0.08,0.58) 0.8910		
M1000 BID (n=170)	-1.40 (0.14)				
M500 BID (n=171)	-0.90 (0.14)				

Note: Model includes baseline HbA1c as linear covariate and baseline eGFR, region, treatment as fixed effects. Missing data are imputed using multiple imputation and all observed cases of change from baseline at week 24 weeks are treated as non-missing.
*non-inferiority test at alpha=0.025 with the specified margin of 0.35%

Source: Excerpted from Dr. Sinks' Statistical Review

Dr. Sinks' has concluded that combination therapy with empagliflozin and metformin is statistically significantly superior with regard to reduction in HbA1c from baseline after 24 weeks. Though the statistical analysis performed by the applicant only utilized the population that remained on treatment, additional sensitivity analyses performed by the applicant and by the FDA statistical reviewer resulted in the same conclusion. This leads me to believe that the finding is robust.

The next step in the statistical testing hierarchy was comparison of empagliflozin (first at 25 mg, and then at 10 mg) to metformin 1000 mg BID. Both approaches (i.e., applicant's and FDA's) did not demonstrate non-inferiority of empagliflozin to metformin 1000 mg BID (pre-specified non-inferiority margin of 0.35%). As non-inferiority of empagliflozin (at either dose) to metformin 1000 mg BID was not demonstrated, all formal statistical testing was stopped at this point. All subsequent endpoints are most appropriately considered exploratory. Dr. Sinks does not discuss the secondary endpoints further, but the applicant's findings for the secondary endpoints are briefly discussed in section 6.1.5 of Dr. Ondina Lungu's Clinical Review, and are summarized below:

- Treatment with combination therapy yielded a numerically greater reduction in fasting plasma glucose compared to the individual components at 24 weeks.
- Treatment with combination therapy yielded a numerically greater reduction in body weight compared to the individual components at 24 weeks.

Other endpoints considered for efficacy by the applicant included change in HbA1c over time, categorical HbA1c response, change in blood pressure from baseline, percentage of subjects achieving a composite endpoint, change in waist circumference, and use of rescue medication. Dr. Lungu briefly discusses these endpoints in the Clinical Review, and some of the findings are summarized below:

- Change in HbA1c plateaued at 12 weeks.
- Treatment with combination therapy led to a numerically greater percentage of patients achieved categorical responses compared to the individual components, though the difference was greater when compared to empagliflozin than when compared to metformin.
- Treatment with combination therapy led to a numerically greater change in blood pressure compared to the individual components.

These secondary and other endpoints cannot be considered statistically significant, and the clinical relevance of the findings is unclear.

8. Safety

In Dr. Ondina Lungu's Clinical Review, the safety findings were noted to be consistent with the approved labeling. No new safety signals were identified in the combination use arms, and concomitant use of empagliflozin and metformin did not appear to result in an increased risk to patients.

One death occurred after initiation of study drug. This was a subject treated with empagliflozin 25 mg once daily who died due to suicide. The death occurred 25 days after the last dose of study drug. Though no narrative was submitted for this death, Dr. Lungu does not have concerns that this is due to study drug based on the timing of the event and as it is a single case she does not believe it raises concerns with the study drug. There were no other deaths reported after initiation of study drug.

The incidence of adverse events is summarized in Table 1. The incidence of serious adverse events (SAEs) was highest in the arm treated with empagliflozin 12.5 mg and metformin 500 mg twice daily (6 subjects [3.5%]). Combination therapy yielded a slightly higher incidence for hypoglycemia compared to individual therapy. However, none of the hypoglycemia events qualified as a severe hypoglycemic event (i.e., requiring active assistance to administer carbohydrates, glucagon, or other resuscitative actions). Urinary tract infections seemed to occur with at a slightly higher incidence in the combination treatment arms, while genital infections occurred at the greatest incidence in the empagliflozin 10 mg arm. No clear difference in the incidence of volume depletion events was seen, either using the applicant's custom MedDRA query or a modified MedDRA query that included the additional preferred terms of "dizziness", "vertigo", and "loss of consciousness". There was also no clear imbalance in the incidence of fractures. Though no fractures occurred in the metformin arms, the number of events from the study was small, limiting interpretation of the findings. Similarly, nothing can be said with regard to ketoacidosis, malignancy, or cardiovascular events due to either the absence of or limited numbers of events.

Dr. Lungu has also considered the potential for adverse renal effects and for adverse liver effects. These types of events were generally captured by reported adverse events and by examination of laboratory tests. The results of study 1276.1 do not raise any concerns for adverse renal or liver effects with combination therapy compared to treatment with the individual drug products. The reported laboratory test findings were consistent with what has been previously described.

Dr. Lungu believes that the safety data from this study are consistent with the current labeling and does not recommend adding or removing any safety language based upon review of study 1276.1. I agree with Dr. Lungu that there does not appear to be any new safety concerns based upon the results of this study. The currently approved labeling appears to sufficiently describe the safety profile of empagliflozin.

Table 1: Incidence of selected types of adverse events

	12.5/1000 BID		12.5/500 BID		5/1000 BID		5/500 BID		25 QD		10 QD		1000 BID		500 BID	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	171	100	170	100	171	100	169	100	167	100	172	100	169	100	171	100
SAE	2	1.2	6	3.5	3	1.6	2	1.2	3	1.8	1	0.6	3	1.8	3	1.8
Hypoglycemia	6	3.5	5	2.9	2	1.2	4	2.4	1	0.6	2	1.2	4	2.4	2	1.2
- Severe Hypo	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- Doc symp < 54	0	0	1	0.6	0	0	0	0	0	0	0	0	0	0	0	0
Urinary tract infections	22	12.9	20	11.8	14	8.2	11	6.5	15	9	14	8.1	18	10.7	15	8.8
Genital infections	5	2.9	9	5.3	6	3.5	4	2.4	9	5.4	13	7.6	7	4.1	5	2.9
Volume depletion - BI	3	1.8	0	0	0	0	1	0.6	0	0	0	0	2	1.2	0	0
Volume depletion - FDA	9	5.3	9	5.3	7	4.1	7	4.1	4	2.4	5	2.9	5	3	9	5.3
Fracture	2	1.2	2	1.2	2	1.2	0	0	1	0.6	1	0.6	0	0	0	0
Cardiovascular events[1]	1	0.6	0	0	0	0	0	0	0	0	0	0	1	0.6	0	0
Ketoacidosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Malignancies	1	0.6	1	0.6	0	0	0	0	0	0	0	0	0	0	0	0

[1] includes only those events that were positively adjudicated

12.5/1000 BID = empagliflozin 12.5 mg and metformin 1000 mg twice daily; 12.5/500 BID = empagliflozin 12.5 mg and metformin 500 mg twice daily; 5/1000 BID = empagliflozin 5 mg and metformin 1000 mg twice daily; 5/500 BID = empagliflozin 5 mg and metformin 500 mg twice daily; 25 QD = empagliflozin 25 mg once daily; 10 QD = empagliflozin 10 mg once daily; 1000 BID = 1000 mg twice daily; 500 BID = 500 mg twice daily; SAE = serious adverse event; Severe Hypo = hypoglycemia requiring active assistance to administer carbohydrates, glucagon, or other resuscitative actions; Doc symp < 54 = symptomatic hypoglycemia with documented blood glucose < 54 mg/dL; Volume depletion – BI = volume depletion assessment using applicant's custom MedDRA query; volume depletion – FDA = volume depletion assessment using a modified custom MedDRA query which consists of the applicant's MedDRA query plus events with terms of "dizziness", "vertigo", and "loss of consciousness"

Source: Adapted from Table 17, Table 19, Table 25, Table 26, Table 29, Table 30, and section 7.4 of Dr. Lungu's Clinical Review, and Table 15.3.1.9: 1 of the study report for study 1276.1

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(b) (4)

9. Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting was held to discuss either supplement.

10. Pediatrics

Not applicable. No data on use in pediatrics were included.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

- Labeling comments relevant to both supplements:

  As discussed above, the applicant has proposed to include language in (b) (4) section 12.3, and (b) (4) of the label.

  I do not believe that the additional information that the applicant proposes to include in (b) (4) warrants inclusion and (b) (4)

  I agree with the proposed language for section 12.3. The language here summarizes the information from an in vitro study. Dr. Sista agrees with the applicant's conclusions from the study data and finds the language acceptable. The edited language is below (additions are underlined, deletions are struck-through):

  (b) (4)

  I do not agree with including the proposed language in (b) (4). The available data do not adequately support that the (b) (4).

- Labeling comments for JARDIANCE (NDA-204629):

  Acknowledging that the results of this study showed that combination therapy was statistically significantly better than individual therapy, I do not find the study design or results to be relevant to the empagliflozin label. The study design is informative for the empagliflozin and metformin combination product, and less so for the empagliflozin monoproduct.

  The applicant was asked to provide a rationale for the relevance of study 1276.1 for the empagliflozin label, and a response was received on February 23, 2016. In the

response, applicant states that the study provides useful information on the efficacy of empagliflozin in combination with metformin as initial therapy in treatment naïve patients. The applicant also points to regulatory precedent for including factorial design studies in the labeling for individual components of the fixed dose combination product. While the dose was administered as a divided dose in study 1276.1, the applicant notes that comparability between a once daily dose and the same dose given in two divided dose has been shown.

While I continue to question the relevance of this study for the empagliflozin label, but given precedent for including such a study in another member of the class and in the empagliflozin label I accede to the applicants proposal to add this study. (b) (4) [redacted] I would favor a limited discussion of study 1276.1 for the empagliflozin label, similar to the presentation of the empagliflozin and linagliptin factorial study (i.e., study 1275.1) that is already labeled.

- Labeling comments for SYNJARDY (NDA-206111):

The submitted data support the proposed change in language to the indication. I agree with changing the indication from:

"…as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin."

to:

"… as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate."

(b) (4) [redacted]

Additional comments on the label for SYNJARDY (NDA-206111) with respect to the Pregnancy and Lactation Labeling Rule are pending consultation with the Division of Pediatric and Maternal Health.

Labeling negotiations are ongoing, and final labeling may differ from these recommendations.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval for both of these supplements, pending agreement on labeling language.

- Risk Benefit Assessment

The data submitted do not change the risk-benefit profile of either NDA product. The data continues to suggest that use of the drug product improves glycemic control. This in turn is expected to result in improved clinical outcomes. The risks associated with therapy remain consistent with the current labeling, and no new safety signals are identified from the submitted data which would alter the current risk-benefit assessment.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable. I do not recommend a Risk Evaluation and Management Strategy.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable. I do not recommend any additional post-marketing requirements or commitments.

- Recommended Comments to Applicant

I do not have any additional comments to the applicant.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H CHONG
03/18/2016

JEAN-MARC P GUETTIER
03/18/2016
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s005

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	NDA-204629, Suppl-5, SDN 246/ NDA 206111, Suppl-1, SDN 38
Priority or Standard	Standard
Submit Date(s)	May 20, 2015/ September 11, 2015
Received Date(s)	May 20, 2015/ September 11, 2015
PDUFA Goal Date	March 20, 2016 / July 11, 2016
Division / Office	DMEP
Reviewer Name(s)	Andreea O. Lungu
Review Completion Date	February 5, 2016
Established Name	Empagliflozin / Empagliflozin and metformin hydrochloride
Trade Name	Jardiance / Synjardy
Therapeutic Class	Sodium-dependent glucose co-transporter-2 inhibitor Sodium-dependent glucose co-transporter-2 inhibitor and biguanide
Applicant	Boehringer Ingelheim Pharmaceuticals Inc.
Formulation(s)	Oral Tablet
Dosing Regimen	NDA-204629: Once daily: 10 mg and 25 mg empagliflozin NDA-206111: Twice daily: 5 mg / 500 mg, 5 mg / 1000 mg, 12.5 mg / 500 mg, 12.5 mg / 1000 mg (empagliflozin / metformin hydrochloride)

Indication(s)	NDA-204629: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus NDA-206111 (proposed): Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate
Intended Population(s)	Adults with Type 2 Diabetes Mellitus
Team Leader	William H. Chong
Division Director	Jean-Marc Guettier
Statistical Reviewer - Efficacy	Susie Sinks
Project Manager	Michael G. White

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Abbreviations

ADA	American Diabetes Association
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
CEC	Clinical events committee
CHF	Congestive heart failure
CI	Confidence interval
CMQ	Customized MedDRA query
CV	Cardiovascular
CVOT	Cardiovascular outcomes trial
CTD	Common technical document
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DPP-4	Dipeptidyl peptidase-4
eCTD	Electronic Common Technical Document
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
Empa	Empagliflozin
FAS	Full analysis set
FAS (OC)	Full analysis set, observed cases
FDA	Food and Drug Administration
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c/glycosylated hemoglobin
HDL	High density lipoprotein cholesterol
HLT	Medical Dictionary for Regulatory Activities High Level Term
ICH	International Conference on Harmonisation

ICH E3	International Conference on Harmonisation: Structure and content of clinical study reports
IND	Investigational new drug
LDL	Low density lipoprotein cholesterol
LL	Lower limit
LLRR	Lower limit of the reference range
LOCF	Last observation carried forward
LVOT	Last value on treatment
MACE	Major adverse cardiovascular event
MAED	MedDRA Adverse Event Diagnostics
MDI	Multiple daily injections (insulin)
Mdn	Median
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory activities
Met	Metformin
MI	Myocardial infarction
MMRM	Mixed-effects model repeated measures
NA	Not applicable
NCF	Noncompleters considered failure
NDA	New Drug Application
Non-HDL	Non-high density lipoprotein cholesterol
NR	Not reported
PG	Plasma glucose
PI	Principal investigator
PK	Pharmacokinetics
PPS	Per-protocol set
PT	Medical Dictionary for Regulatory Activities Preferred Term
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2	Sodium-dependent glucose co-transporter-2
SMQ	Standardized Medical Dictionary for Regulatory Activities Query

SOC	Medical Dictionary for Regulatory Activities System Organ Class
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
TIA	Transient ischemic attack
TS	Treated set
TZD	Thiazolidinedione
ULN	Upper limit of normal
ULRR	Upper limit of reference range
WRR	Within the reference range

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant has submitted efficacy supplements based on the results of a completed clinical study (1276.1) providing data about the treatment effects of concomitant therapy with empagliflozin and metformin in treatment-naïve patients with type 2 diabetes mellitus (T2DM). The intent of this submission is to support the existing Indications and Usage sections of the approved labeling for the Jardiance (empagliflozin) and to support an updated Indication for Synjardy (empagliflozin and metformin hydrochloride).

Based on my review of the data, I am recommending approval of both these efficacy supplements.

1.2 Risk Benefit Assessment

The current efficacy supplements report data from study 1276.1, in which twice daily administration of empagliflozin+metformin was compared with the dose-matched individual components of empagliflozin or metformin in drug-naive patients with T2DM. The same study was submitted for both NDA 204629 (empagliflozin) and NDA 206111 (empagliflozin-metformin fixed-dose combination).

Empagliflozin is approved for use in adults with T2DM at the doses of 10 mg and 25 mg daily. The risk-benefit assessment was discussed at the time of the original NDA approval in the clinical review by Dr. Chong. In the original NDA submission, empagliflozin was shown to be effective in reducing glycosylated hemoglobin (HbA1c) as monotherapy, and as add-on to a variety of antidiabetic regimens (including metformin, metformin plus sulfonylureas, pioglitazone, and basal insulin).

Metformin is an oral biguanide, which decreases production of hepatic glucose, intestinal glucose absorption and improves insulin sensitivity. It was approved for the treatment of T2DM in US as Glucophage (NDA 20357) on March 3, 1995.

The empagliflozin-metformin combination was approved for use in adults with T2DM at the following twice daily doses: 5 mg empagliflozin/500 mg metformin hydrochloride 5 mg empagliflozin/1000 mg metformin hydrochloride 12.5 mg empagliflozin/500 mg metformin hydrochloride 12.5 mg empagliflozin/1000 mg metformin hydrochloride.

In this submission, the Applicant has shown that the empagliflozin-metformin combination treatment groups resulted in a decrease in HbA1c from baseline to 24 weeks that was greater than the change observed with the corresponding doses for the individual components. However, a few issues are notable:

- Subpopulations analyses showed that, for the combination treatment groups containing metformin 1000 mg bid (M1000 bid), the combination therapy was not always superior to the M1000 bid monotherapy group.
- The point estimate for the difference between the combination therapy groups containing metformin 1000 mg bid and the metformin 1000 mg bid arm is small, with the upper bound of the 95% CI close to 0.
- Empagliflozin 25 mg qd (E25 qd) and empagliflozin 10 mg qd (E10 qd) failed to show non-inferiority to M1000 bid.
- In the combination arms, empagliflozin was studied as a bid drug rather than the qd formulation that is currently FDA approved. The applicant did provide efficacy bridging between once daily dosing of empagliflozin to twice daily dosing of empagliflozin (study 1276.10) that was reviewed in the NDA for the fixed dose combination product (empagliflozin-metformin), and was deemed adequate.

Keeping the above issues in mind, however, I did not identify any new safety signals in the review of the study 1276.1 that would preclude the combined use of empagliflozin with metformin in treatment-naïve patients with T2DM, and the study met its primary endpoint. Safety findings with the empagliflozin component include increased risk for urogenital infections, volume depletion/hypotension, and decreases in renal function. There were some concerning laboratory findings such as increases in low-density lipoprotein cholesterol with empagliflozin, but the significance of these observations is not known. In addition, there was no evidence of new or more concerning safety signals with twice daily vs. once daily dosing.

The safety findings from this study are consistent with the current prescribing information for empagliflozin.

Based on these findings, I believe that the overall findings from study 1276.1 support the efficacy of empagliflozin in combination with metformin, and do not alter the favorable risk-benefit profile that led to empagliflozin and empagliflozin-metformin fixed-drug combination FDA approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Empagliflozin is a sodium-dependent glucose co-transporter-2 (SGLT2) inhibitor approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, a disease of impaired glucose regulation due to impaired insulin action and insulin resistance. Management of T2DM focuses on glycemic control, and involves lifestyle changes (diet and exercise) as well as use of currently available antidiabetic drugs. SGLT2 is a transporter found in the proximal renal tubule, and is responsible for renal glucose reabsorption. Inhibition of this transporter increases glucosuria, which in turn results in improved glycemic control.

2.1 Currently Available Treatments for Proposed Indications

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes include:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 (GLP-1) analogues
- SGLT2 inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrant (i.e. colesevelam hydrochloride)

Despite the number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug. Further, many of these drug classes may not be tolerated or have limited usefulness in certain populations. For example, sulfonylureas (SU) and insulin are associated with a higher risk for hypoglycemia, thiazolidinedione's (TZDs) may be associated with edema and are not for use in many patients with congestive heart failure, while metformin and sodium-glucose co-transporter 2 (SGLT2) inhibitors are contraindicated in patients with severe renal dysfunction. TZDs, SUs, and insulin

are all associated with significant weight gain. Additionally, progressive β-cell dysfunction may lead to secondary treatment failure to the anti-diabetic therapy over time requiring the addition of other agents. For these reasons, and because T2DM is a disease that is heterogeneous in both pathogenesis and clinical manifestation, there is an unmet need for new anti-diabetic therapies and concomitant treatment options for T2DM in patients who are not adequately controlled on monotherapy.

2.2 Availability of Proposed Active Ingredient in the United States

Empagliflozin and the empagliflozin + metformin combination drug product are approved for marketing in the United States, and are available by prescription. Empagliflozin is also a component of a fixed-dose combination product with linagliptin.

2.3 Important Safety Issues with Consideration to Related Drugs

There are three SGLT2 inhibitors currently approved by the FDA: empagliflozin, dapagliflozin, and canagliflozin.

Safety concerns related to the class include hypotension, diabetic ketoacidosis (DKA), urosepsis and urinary tract infections, genital mycotic infections, decreases in renal function, and increases in hematocrit and cholesterol.

Canagliflozin was approved by the FDA on March 29, 2013. Issues discussed at the Advisory Committee for canagliflozin included reduced efficacy with impaired renal function, development of decreased renal function and renal adverse events (including hyperkalemia), volume depletion events, changes in bone turnover markers, an imbalance in fractures (especially in upper limb fractures), increased risk of genital mycotic infections, effects on lipids (i.e. increases in low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and non-HDL), and an imbalance in early cardiovascular (CV) events. Post-marketing requirements for canagliflozin include a cardiovascular outcomes study, a bone safety study, and an enhanced pharmacovigilance program for reports of malignancy (pheochromocytoma, Leydig cell tumor, and renal cell carcinoma), fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy.

A Complete Response was issued for dapagliflozin on January 17, 2012 due to concerns that included malignancy (specifically bladder cancer) and liver toxicity. On July 11, 2013, the NDA was re-submitted, and dapagliflozin was approved by the FDA on January 8, 2014 following an Advisory Committee meeting that discussed cardiovascular risk, malignancy risk, and liver

toxicity issues. Post-marketing requirements include a cardiovascular outcome study (with the protocol amended to include additional evaluation of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, complicated genital infections, complicated urinary tract infections [e.g. pyelonephritis, urosepsis], serious events related to hypovolemia and serious hypersensitivity reactions).

Empagliflozin was approved on August 1, 2014. Post-marketing requirements include a cardiovascular outcomes trial including evaluation of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions.

Serious concerns regarding a potential for ketoacidosis and serious urinary tract infections were identified in the post-marketing setting for this class, resulting in a safety labeling change for all approved SGLT2 inhibitors on December 4, 2015

2.4 Summary of Presubmission Regulatory Activity Related to Submission

The initial protocol for study 1276.1 was submitted April 30, 2012, followed by two global and three local amendments.

The first global amendment was dated December 13, 2012, approximately 5 weeks after the start of the trial. The main change introduced by this amendment was related to changing HbA1c upper and lower limits. Until the first global amendment, patients with HbA1c >10.0% were to be enrolled in an open-label (OL) group. After the introduction of the amendment, all eligible patients were randomized to one of the eight double-blind treatment groups. Further enrollment into OL group was stopped. In addition, the main analysis for the primary and key secondary endpoint was updated following an FDA request to change the approach to missing data.

The second global amendment was introduced on March 6, 2015, approximately 1.3 years after trial start. The main changes introduced by this amendment were related to the planned study results analyses and had no direct impact on how patients were handled during study conduct. The definition of reporting of AEs was changed to reflect new company guidelines. Selected hepatic and cancer cases were to be sent for adjudication to committees specially formed to assess such cases.

In addition, a total of 3 local amendments (in Canada, France, and Germany) were issued based on local health authority requests and all required and obtained IEC/IRB/competent authority approval before implementation with minor clarifications submitted as amendments.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Based on review of the submitted study report, there are no apparent issues with data integrity or with the integrity of study conduct.

3.2 Compliance with Good Clinical Practices

The Applicant states that all clinical studies followed the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), and conformed to the Declaration of Helsinki.

3.3 Financial Disclosures

While one investigator disclosed significant compensation or equity interest in the company, it is unlikely that this substantially impacted the findings from the study. See 1.1 for the completed Financial Disclosure Review Template.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no new CMC information included in this supplement.

4.2 Clinical Microbiology

There is no information related to clinical microbiology included in this supplement.

4.3 Preclinical Pharmacology/Toxicology

There is no new pharmacology/toxicology information included in this supplement.

4.4 Clinical Pharmacology

The following study was included as part of this submission:

"In vitro evaluation of empagliflozin as an inhibitor of human UDP-glucuronosyltransferase enzymes: Determination of IC50 and Ki values and assessment of drug interaction potential".

Please see the dedicated clinical pharmacology review by Dr. Sang Chung for details:

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

For this efficacy supplement, the Applicant has submitted a complete study report for study 1276.1 to support labeling for use of the dual therapy empagliflozin-metformin in drug naïve patients with T2DM when both metformin and empagliflozin are appropriate. This randomized, double-blind, parallel group study compared the efficacy and safety of twice daily oral administration of empagliflozin+metformin vs the individual components of empagliflozin and metformin in drug-naïve patients with type 2 diabetes. As only a single study was submitted to support these supplements, it will not be presented as a table.

5.2 Review Strategy

This review is based on the 1276.1 study report submitted by the Applicant for NDA 204629, and cross-referenced by NDA 206111, as well as the datasets provided as part of this submission.

All of the submitted narratives for deaths and nonfatal serious adverse events (SAEs) were reviewed. For review of the adverse events, the information presented in the study report was also compared to tabulations generated using the included datasets and using MedDRA Adverse Event Diagnostics (MAED), and JReview.

5.3 Discussion of Individual Studies/Clinical Trials

The Applicant submitted only one study report (Study 1276.1) in support of the two efficacy supplements for NDA 204629, and NDA 206111. This is a pivotal Phase III trial, intended to support approval for empagliflozin and metformin fixed dose combination (FDC) therapy as dualdual initial therapy in drug-naïve patients with type 2 diabetes mellitus. The study design is summarized below in this section.

Study Title: A 24-week phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug-naïve patients with type 2 diabetes mellitus.

Study Design:
This is a randomized, double-blind, double-dummy, multi-national, parallel group study. It was designed to investigate the efficacy, safety, and tolerability of the combination of empagliflozin (12.5 mg bid or 5 mg bid) and metformin immediate release (1000 mg bid or 500 mg bid) compared to the corresponding individual components (empagliflozin 25 mg qd, empagliflozin 10 mg qd, metformin 1000 mg bid, and metformin 500 mg bid) after 24 weeks of treatment in patients with type 2 diabetes mellitus and insufficient glycemic control, despite diet and exercise.

The Sponsor chose a factorial design for this trial as advised by the FDA, in order to request the following indication: "as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both empagliflozin and metformin is appropriate".

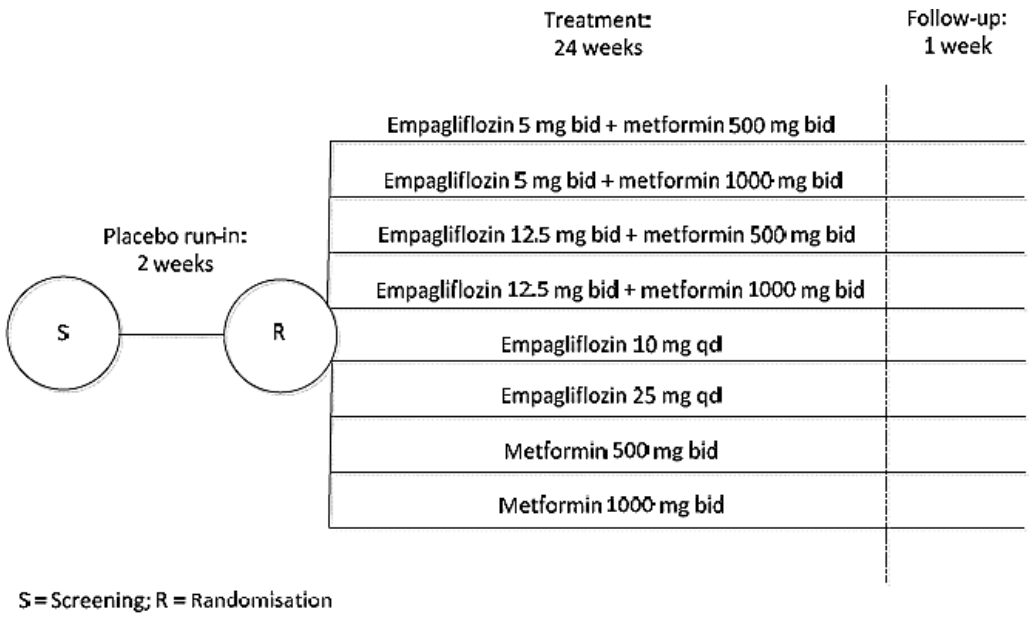
As presented in Figure 1, all patients underwent a two-week single-blinded placebo run-in period followed by randomization to one of the eight treatment arms in a 1:1:1:1:1:1:1:1 ratio.

Before the first global protocol amendment, patients with a screening HbA1c value between 7 and 10% were eligible for entering the placebo run-in period. Patients with HbA1c >10% were to be enrolled in an open-label (OL) group. After the amendment, patients suitable after screening and with HbA1c between 7.5 and 12% inclusive were to undergo a two-week single-blinded placebo run-in period prior to randomization. Patients who successfully completed this period and still met the inclusion/exclusion criteria were randomized to the 24-week treatment period of the study, in which they were to receive either one of the doses of empagliflozin or metformin or a combination of the two. The same treatment periods were used for the patients in the open label group.

The randomization was stratified by the following factors:
- Screening HbA1c value (<8.5%, ≥8.5%);
- Screening eGFR (≥ 90 mL/min, <90 mL/min);
- Region (Europe, Asia, North America, Latin America)

The patient participation in the study was concluded when they completed the last planned study visit. The time period for which adverse events (AEs) were still considered on treatment was up to 7 days following last intake of trial medication. All AEs, including those persisting at the patient's last visit, were followed up for up to 30 days, and it was to be confirmed if they had resolved or had been sufficiently characterized.

Figure 1 Trial Design



Source: Figure 9.1:1 Overview of the Trial Design, 1276.1 Study Report Body

Duration of Main Study:

The randomized treatment period for the study was 24 weeks.

Inclusion criteria included:

- Drug-naive adults with a diagnosis of T2DM
- HbA1c at baseline ≥ 7.5% and ≤ 12%
- BMI at baseline ≤ 45 kg/m^2

Exclusion criteria included:

- Uncontrolled hyperglycemia with a glucose level >240 mg/dl (>13.3 mmol/l) after an overnight fast and confirmed by a second measurement (not on the same day)
- Acute coronary syndrome (non-STEMI, STEMI, and unstable angina pectoris), stroke, or transient ischemic attack (TIA) within 3 months prior to consent
- Any antidiabetic drug for 12 weeks prior to randomization.
- Liver disease, defined by serum levels of either alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase above three times upper limit of normal (ULN) as determined during screening or run-in period

- Impaired renal function, defined as GFR <60 ml/min (MDRD formula) as determined during the screening period and/or during the run-in period
- Bariatric surgery within the past 2 years and other gastrointestinal surgeries that can induce chronic malabsorption
- Known blood dyscrasias or any disorders causing hemolysis or unstable red blood cell (e.g. malaria, babesiosis, hemolytic anemia)
- Treatment with anti-obesity drugs 3 months prior to informed consent or any other treatment at the time of screening (i.e. surgery, aggressive diet regimen, etc.) leading to unstable body weight
- Current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM
- For Canada only: active history of genito-urinary infection within 2 weeks prior to the informed consent

For full inclusion and exclusion criteria, refer to the study protocol. The inclusion/exclusion criteria are acceptable for this type of study.

Investigational drug dosing:

Metformin: Dose escalation was applied to metformin dosing. Patients assigned to treatment with the empagliflozin 12.5 mg bid + metformin 1000 bid (E12.5+M1000 bid), empagliflozin 5 mg bid + metformin 1000 bid (E5+M1000 bid), or metformin 1000 bid (M1000 bid) were administered metformin 500 mg bid in the first week of treatment, 850 mg bid in the second week of treatment, and 1000 mg bid in the third week of treatment.

Empagliflozin: No dose escalation was applied for empagliflozin dosing. Patients assigned to treatment with empagliflozin initiated at the assigned dose.

Glycemic Rescue:

Rescue medication for treating hyperglycemia could be initiated during the double-blind treatment period of the trial (i.e. from Visits 3-7) whenwhen the criteria below were met:

- Week 1 – 12 (i.e. up to and including the result from Visit 5), if the patient had a glucose level > 240 mg/dL (> 13.3 mmol/l) after an overnight fast;
- Week 12 – 24 (i.e. from the day after Visit 5 onwards), if the patient had a glucose level > 200 mg/dL (> 11.1 mmol/l) after an overnight fast.

The above results were to be confirmed, meaning there was a minimum of 2 measurements, at least one of which was to be performed after an overnight fast at the investigational site, and on a different day from the initial (overnight fasting) measurement. The choice of rescue medicationinitiated was at the Investigator's discretion. A fasting glucose sample and an HbA1c sample (unless one was available within the preceding 4 weeks) were to be obtained before initiation of rescue therapy and sent to the central lab for analysis.

Subjects were identified as "rescued" if one of the following occurred:

- additional antidiabetic medication used for ≥7 consecutive days or until premature discontinuation of trial medication;
- the patient discontinued trial medication prematurely due to lack of efficacy (including hyperglycemia reported as AE) and the patient started an additional antidiabetic medication on the next day

Patients continued participation in the trial if rescue medication was required, and rescue medication could be used from when it was initiated until the end of the trial. The choice of rescue medication and its dosage was left to the discretion of the Investigator. However, other SGLT-2 inhibitors (if available) and metformin were not to be used as rescue medication. In case of repeated symptomatic hypoglycemia or severe hypoglycemia, appropriate adjustment of oral antidiabetic therapy, such as a dose reduction/discontinuation of ongoing rescue medication was to be initiated.

If no further effect from the rescue medication was anticipated and the patient's hyper- or hypoglycemia could not be controlled in the investigator's clinical opinion, the study medication was to bediscontinued.

Primary Endpoint:

- Change in HbA1c from baseline after 24 weeks of treatment

Secondary endpoints:

- Change from baseline in fasting plasma glucose after 24 weeks of treatment
- Change from baseline in body weight after 24 weeks of treatment

Further efficacy endpoints in this trial were:

- HbA1c:
    - Occurrence of a treat-to-target efficacy response, that is an HbA1c of <7.0% (<53.0 mmol/mol) after 24 weeks of treatment;

  - Occurrence of a relative efficacy response (HbA1c lowering by at least 0.5% [5.5 mmol/mol]) after 24 weeks of treatment;
  - Change from baseline in HbA1c by visit over time.
- FPG: change from baseline by visit over time;
- Body weight: percentage change from baseline to Week 24;
- Waist circumference: change from baseline to Week 24;
- Systolic and diastolic BP (SBP and DBP): change from baseline to Week 24;
- Composite endpoint of the following conditions at Week 24, with all 3 criteria fulfilled:
  - HbA1c reduction of at least 0.5%,
  - SBP reduction of more than 3 mmHg,
  - Body weight reduction of more than 2%.

6 Review of Efficacy

Efficacy Summary

The efficacy of combining empagliflozin with metformin as therapy for drug-naïve patients with T2DM was assessed in a single factorial design study (study 1276.1). The primary efficacy endpoint was met, meaning that the combination of empagliflozin and metformin, at any dose level, showed superiority when compared to the corresponding individual components in terms of HbA1c reduction at 24 weeks.

A few issues around the primary efficacy endpoint warrant discussion. First, the point estimate of the adjusted mean difference between the combination therapy groups and the M1000 bid monotherapy treatment group was relatively small, and the upper bound of the 95% confidence interval was close to zero. This brings into question whether the difference is clinically meaningful. Additionally, the subpopulation analyses were not always supportive of the primary analysis particularly when comparing the combination therapy groups that contained M1000 bid and the M1000 bid monotherapy group. Notably, using the MMRM imputation method, the E12.5+M1000 bid group was not different when compared to the M1000 bid group in any geographical region In addition, the combination treatment groups containing M1000 bid were no better than M1000 bid monotherapy group in patients age >65, with HBA1c at baseline >8.5%, eGFR 60 to < 90 ml/min/1.73 m^2, or diabetes history for one year or less, or more than 5 years. While it is reasonable that this could be due to chance considering that the subgroups are small, I remain concerned that, at least in certain populations, there may not be any additional efficacy benefit in starting dual therapy with empagliflozin and metformin rather than metformin alone at the 1000 mg bid dose in treatment-naïve patients.

Comparison of empagliflozin monotherapy to metformin monotherapy was part of the testing hierarchy. Both empagliflozin arms failed to demonstrate non-inferiority to M1000 bid in lowering HbA1c at 24 weeks with a pre-set non-inferiority margin of 0.35%. As a result, the subsequent secondary endpoints were analyzed as exploratory. The changes in FPG and weight at 24 weeks were overall greater with the dual therapy compared to the corresponding individual components, and the weight loss in the groups containing empagliflozin was greater when compared to the metformin monotherapy treatment groups.

No clear dose response was observed for empagliflozin, a finding that is in line with the conclusions of the original empagliflozin NDA review by Dr. William Chong.

6.1 Indication

Empagliflozin is approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The Applicant does not propose any changes to the indication for empagliflozin with this efficacy supplement. For the fixed dose combination empagliflozin-metformin product, the Applicant is proposing to change the indication such that that the combination will be used as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both empagliflozin and metformin is appropriate.

6.1.1 Methods

For the review of efficacy, I reviewed the study report for study 1276.1.

The primary efficacy endpoint for this study was change from baseline in HbA1c at 24 weeks. For discussion of the FDA's analysis of the efficacy data, see the dedicated statistical review by Dr Susie Sinks.

The Applicant created the following analysis populations:

Population	Description	Number of subjects
Screened set (SCR)	All patients screened for trial, with informed consent, and completing at least one screening procedure at visit 1	2,482
Randomized set (RS)	All patients from SCR randomized to double-blind treatment, regardless of whether any study drug was administered	1,364
Treated set (TS)	All patients treated with at least one dose of randomized study drug	1,360
Treated set actual (TS actual)	All patients treated with at least one dose of randomized study drug (assigned to treatment based on actual treatment received)	1,360
Full analysis set (FAS)	All randomized patients treated with at least one dose of trial	1,327

	medication, with a baseline and at least 1 on-treatment HbA1c assessment	
Full analysis set – completers (FAS completers)	All patients from the FAS that did not prematurely discontinue trial medication and completed at least 161 days of treatment.	1,217
Per-protocol set (PPS)	All patients from the FAS without important protocol violations (IPVs) which would lead to exclusion from this set	1,209
Open label set (OLS)	All patients in the open-label treatment arm	53

For the analysis of efficacy, the Applicant used the FAS population.

The primary analysis performed by the Applicant was a restricted maximum likelihood (REML)-based missed model repeated measures (MMRM) approach, and was performed on the full analysis set (FAS) with observed cases (OC) imputation. This approach means that only the available data that were observed while patients were on treatment were included in the analysis, and that missing data were handled implicitly by the statistical model, rather than using any imputation. All values measured after rescue medication taken were considered missing . The statistical reviewer had reservations with this approach as it does not evaluate an intention-to-treat estimand, i.e., the difference in HbA1c change in all randomized patients regardless of treatment adherence to treatment or use of rescue. See Dr. Sinks' review for further discussion of this concern.

The model included effects accounting for the following sources of variation: 'baseline HbA1c' as linear covariate and 'treatment', 'baseline renal function', 'region', 'visit', and 'visit by treatment interaction' as fixed classification effects. The term "baseline HbA1c" refers to the last HbA1c assessment prior to the administration of any randomized study medication. For each patient, the error terms from all the visits represented the within-patient variability and were assumed to follow a multivariate normal distribution with an unstructured covariance matrix.

For superiority of the combination therapy to the individual components, a hierarchical testing procedure at alpha=0.05 (two-sided) was used. The hierarchical testing procedure consisted of eighteight hypotheses for superiority testing of the primary endpoint grouped into dose levels as follows: E12.5+M1000 bid, E12.5+M500 bid, E5+M1000 bid, and E5+M500 bid. Within each dose level, there were 2 hypotheses: one tested whether the combination of empagliflozin and metformin was superior to the corresponding empagliflozin component, and the other tested whether the combination was superior to the corresponding metformin component. The hypotheses at the next dose level were tested in a confirmatory way only if both null hypotheses at the previous dose level were rejected.

Testing for non-inferiority of E25 qd and E10 qd against M1000 bid was introduced by the Applicant for the change from baseline in HbA1c in the second global protocol amendment, and were tested with a non-inferiority margin of 0.35%.

The same REML-based MMRM approach performed on the FAS (OC) was used by the Applicant for analysis of secondary endpoints.

The Applicant performed sensitivity analyses on the per protocol set (PPS) (OC), FAS-completers (OC), and FAS (OC-IR) (OC including values after initiation of rescue therapy) to assess the impact of important protocol violations, and premature discontinuation of the study medication on the primary endpoint. A further sensitivity analysis of the treatment effect on the primary endpoint at Week 24 was evaluated using an MMRM – same model as for the primary analysis – but including additionally the baseline HbA1c by visit interaction for the FAS (OC). In addition, an ANCOVA was applied on the FAS (LOCF) at Week 24, with 'baseline HbA1c' as linear covariate and 'region', 'baseline renal function', and 'treatment' as fixed classification effects.

The Applicant reports that, with regard to each efficacy and safety endpoints, the term "baseline" refers to the last observed measurement prior to the administration of any randomized study medication. Screening eGFR is defined as the screening eGFR categories used for the stratified randomization.

6.1.2 Demographics

The demographic and baseline characteristics at screening of all randomized patients are summarized in Table 1 below. Overall, the treatment arms were reasonably well balanced with respect to age, sex, race, ethnicity, and baseline renal function.

The study population consisted of 56.3% males, and most patients (85.9%) were less than 65 years old. Over half (56.2%) of the patients were White, 23.3% were Asian, and 15.7% American Indian/Alaska native. Only 4.7% of patients were Black/African American, and, as a result, interpretation of efficacy in this racial group is limited. Overall, 28.0% of patients were from Latin America, 27.7% were from Europe, 26.1% were from Asia, and 18.3% were from North America.

Most patients had normal renal function (51.8%) or mild renal impairment (45.2%) at baseline. Only 39 patients (2.9%) had baseline eGFR values <60 ml/min/1.73 m^2.

Table 1 Baseline Demographic Data- FAS

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid	Total
Number of patients, N (%)	169 (100.0)	165 (100.0)	167 (100.0)	161 (100.0)	164 (100.0)	169 (100.0)	164 (100.0)	168 (100.0)	1327 (100.0)
Sex, N (%)									
Male	88 (52.1)	105 (63.6)	99 (59.3)	97 (60.2)	83 (50.6)	97 (57.4)	92 (56.1)	86 (51.2)	747 (56.3)
Female	81 (47.9)	60 (36.4)	68 (40.7)	64 (39.8)	81 (49.4)	72 (42.6)	72 (43.9)	82 (48.8)	580 (43.7)
Race, N (%)									
White	94 (55.6)	86 (52.1)	93 (55.7)	88 (54.7)	97 (59.1)	100 (59.2)	95 (57.9)	93 (55.4)	746 (56.2)
Asian	39 (23.1)	40 (24.2)	39 (23.4)	39 (24.2)	35 (21.3)	39 (23.1)	35 (21.3)	43 (25.6)	309 (23.3)
Amer. Indian / Alaska Native	29 (17.2)	30 (18.2)	27 (16.2)	27 (16.8)	24 (14.6)	23 (13.6)	27 (16.5)	22 (13.1)	209 (15.7)
Black / African American	7 (4.1)	9 (5.5)	7 (4.2)	7 (4.3)	8 (4.9)	7 (4.1)	7 (4.3)	10 (6.0)	62 (4.7)
Hawaiian / Pacific Islander	0	0	1 (0.6)	0	0	0	0	0	1 (0.1)
Ethnicity, N (%)									
Not Hispanic / Latino	118 (69.8)	111 (67.3)	109 (65.3)	113 (70.2)	111 (67.7)	117 (69.2)	115 (70.1)	121 (72.0)	915 (69.0)
Hispanic / Latino	51 (30.2)	54 (32.7)	58 (34.7)	48 (29.8)	53 (32.3)	52 (30.8)	49 (29.9)	47 (28.0)	412 (31.0)
Region, N (%)									
Latin America	47 (27.8)	47 (28.5)	47 (28.1)	43 (26.7)	47 (28.7)	48 (28.4)	45 (27.4)	47 (28.0)	371 (28.0)
Europe	45 (26.6)	44 (26.7)	46 (27.5)	47 (29.2)	44 (26.8)	47 (27.8)	47 (28.7)	47 (28.0)	367 (27.7)
Asia	44 (26.0)	44 (26.7)	44 (26.3)	42 (26.1)	42 (25.6)	45 (26.6)	42 (25.6)	43 (25.6)	346 (26.1)
North America	33 (19.5)	30 (18.2)	30 (18.0)	29 (18.0)	31 (18.9)	29 (17.2)	30 (18.3)	31 (18.5)	243 (18.3)
Age [years], mean (SD)	53.6 (10.7)	51.0 (10.7)	52.3 (11.3)	52.2 (11.7)	53.3 (10.7)	53.1 (10.7)	51.6 (10.8)	53.4 (10.9)	52.6 (10.9)
Age, N (%)									
<50 years	59 (34.9)	76 (46.1)	68 (40.7)	66 (41.0)	54 (32.9)	60 (35.5)	64 (39.0)	65 (38.7)	512 (38.6)
50 to <65 years	84 (49.7)	71 (43.0)	70 (41.9)	72 (44.7)	87 (53.0)	86 (50.9)	80 (48.8)	78 (46.4)	628 (47.3)
65 to <75 years	21 (12.4)	14 (8.5)	24 (14.4)	18 (11.2)	23 (14.0)	19 (11.2)	18 (11.0)	19 (11.3)	156 (11.8)
≥75 years	5 (3.0)	4 (2.4)	5 (3.0)	5 (3.1)	0	4 (2.4)	2 (1.2)	6 (3.6)	31 (2.3)
Baseline eGFR (MDRD) [mL/min/1.73m^2], mean (SD)	92.34 (19.24)	94.90 (20.86)	93.59 (21.92)	93.01 (20.51)	91.73 (19.52)	94.00 (21.55)	93.19 (20.20)	90.90 (19.37)	92.96 (20.40)
Baseline eGFR (MDRD) [mL/min/1.73m^2], N (%)									
≥90	94 (55.6)	90 (54.5)	88 (52.7)	84 (52.2)	80 (48.8)	90 (53.3)	82 (50.0)	80 (47.6)	688 (51.8)
60 to <90	69 (40.8)	70 (42.4)	73 (43.7)	74 (46.0)	81 (49.4)	71 (42.0)	80 (48.8)	82 (48.8)	600 (45.2)
45 to <60	6 (3.6)	5 (3.0)	4 (2.4)	2 (1.2)	2 (1.2)	8 (4.7)	2 (1.2)	5 (3.0)	34 (2.6)
<45	0	0	2 (1.2)	1 (0.6)	1 (0.6)	0	0	1 (0.6)	5 (0.4)

Source: Table 10.4.1:1 1276.1 Study Report Body

Table 2 Baseline Efficacy Variables and Other Baseline Characteristics – FAS

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid	Total
Number of patients, N (%)	169 (100.0)	165 (100.0)	167 (100.0)	161 (100.0)	164 (100.0)	169 (100.0)	164 (100.0)	168 (100.0)	1327 (100.0)
HbA_{1c}, mean (SD) [%]	8.66 (1.14)	8.84 (1.31)	8.65 (1.23)	8.68 (1.26)	8.86 (1.29)	8.62 (1.24)	8.58 (1.13)	8.69 (1.04)	8.70 (1.21)
HbA_{1c} category, N (%)									
<8.0%	48 (28.4)	50 (30.3)	57 (34.1)	52 (32.3)	50 (30.5)	58 (34.3)	56 (34.1)	45 (26.8)	416 (31.3)
8.0% to <9.0%	58 (34.3)	42 (25.5)	51 (30.5)	43 (26.7)	38 (23.2)	51 (30.2)	52 (31.7)	62 (36.9)	397 (29.9)
9.0% to <10.0%	38 (22.5)	38 (23.0)	32 (19.2)	39 (24.2)	41 (25.0)	31 (18.3)	35 (21.3)	43 (25.6)	297 (22.4)
≥10.0%	25 (14.8)	35 (21.3)	27 (16.2)	27 (16.8)	35 (21.3)	29 (17.2)	21 (12.8)	18 (10.7)	217 (16.4)
FPG, mean (SD) [mg/dL]	167.8 (40.7)	171.3 (43.5)	163.8 (41.9)	165.9 (39.9)	177.0 (47.8)	169.9 (39.1)	169.9 (48.8)	169.0 (38.9)	169.6 (42.8)
Time since diagnosis of diabetes, N (%)									
≤1 year	98 (58.0)	87 (52.7)	98 (58.7)	95 (59.0)	90 (54.9)	82 (48.5)	90 (54.9)	101 (60.1)	741 (55.8)
>1 to 5 years	45 (26.6)	44 (26.7)	40 (24.0)	48 (29.8)	49 (29.9)	61 (36.1)	48 (29.3)	44 (26.2)	379 (28.6)
>5 to 10 years	16 (9.5)	21 (12.7)	20 (12.0)	15 (9.3)	21 (12.8)	17 (10.1)	16 (9.8)	19 (11.3)	145 (10.9)
>10 years	10 (5.9)	13 (7.9)	9 (5.4)	3 (1.9)	4 (2.4)	9 (5.3)	10 (6.1)	4 (2.4)	62 (4.7)
Body weight, mean (SD) [kg]	83.78 (19.77)	82.87 (18.66)	83.03 (19.15)	82.27 (19.20)	83.08 (20.33)	83.83 (19.80)	83.71 (20.06)	82.66 (21.24)	83.16 (19.75)
Waist circumference, mean (SD) [cm]	101.4 (13.2)	99.4 (13.7)	101.2 (14.6)	100.0 (14.6)	100.7 (16.2)	100.6 (13.3)	101.9 (16.1)	100.2 (15.4)	100.7 (14.7)
SBP, mean (SD) [mmHg]	127.0 (13.7)	127.2 (14.5)	127.2 (13.8)	126.3 (13.0)	128.2 (15.8)	128.4 (14.6)	128.6 (15.5)	127.9 (14.0)	127.6 (14.4)
DBP, mean (SD) [mmHg]	78.5 (8.1)	79.2 (9.1)	78.3 (9.1)	78.4 (8.6)	79.3 (9.4)	79.0 (9.6)	79.1 (9.3)	78.5 (8.6)	78.8 (9.0)

Source: Table 10.4.2:1 1276.1 Study Report Body

There were slight imbalances in the baseline characteristics (Table 2), with fewer patients in the metformin monotherapy groups having a baseline HbA1c above 10%. While the reason for this is unclear, the proportion of patients with HbA1c above 10% was small across treatment groups, and this imbalance is not likely to impact the study results. In all treatment groups, more than 50% of patients had a baseline HbA1c <9%, and between 48.5% and 60.1% had diabetes for 1 year or less at baseline. Baseline blood pressure and body weight were similar between treatment groups.

6.1.3 Subject Disposition

A total of 2,482 patients were screened by 187 centers in 21 countries. Of the 2,482 patients screened, 1,560 patients started the placebo-run in period. Of those, 170 patients were randomized to double-blind treatment with E12.5+M1000 bid, 170 patients to E12.5+M500 bid, 172 patients to E5+M1000 bid, 170 patients to E5+M500 bid, 168 patients to E25 qd, 172 patients to E10 qd, 171 patients to M1000 bid, and 171 patients to M500 bid. Of the 2,482 screened patients, 53 patients were assigned to open-label treatment with E12.5+M1000 bid.

The main reason for not randomizing patients or assigning them to open-label treatment was 'inclusion/exclusion criteria not met' (37.4% of screened patients), most frequently due to 'HbA1c out of range' (26.8% of screened patients).

It is notable that HbA1c eligibility criteria changed after the first protocol amendment to include a wider HbA1c range, and, as a result, no further patients were eligible for the open-label treatment.

A total of 1,360 of the 1,364 randomized patients were treated with double-blind trial medication. Of these, 1,235 patients (90.8%) completed the 24-week treatment period and 125 patients (9.2%) prematurely discontinued trial medication. The most frequent reason for premature discontinuation of the randomized treatment was the occurrence of adverse events (36 patients, 2.6%), with no notable imbalances observed across treatment groups. The reasons for treatment discontinuation in each treatment group are outlined in Table 3 below. Fewer patients in the E12.5+M1000 bid discontinued the trial medication compared to the other groups, the reason is unclear. Notably, more patients in the metformin monotherapy groups discontinued the study medication compared to the patients in the arms containing empagliflozin (Table 3), and it appears that non-compliance, and refusal to continue with the trial medication in the metformin only arms were higher compared to empagliflozin only or combination therapy arms. The rate of adverse events leading to treatment discontinuation was balanced between treatment groups.

Table 3 Disposition of Randomized Patients

	E12.5+M1000 bid N (%)	E12.5+M500 bid N (%)	E5+M1000 bid N (%)	E5+M500 bid N (%)	E25 qd N (%)	E10 qd N (%)	M1000 bid N (%)	M500 bid N (%)	Total random. N (%)
Entered	170	170	172	170	168	172	171	171	1364
Treated	170 (100.0)	170 (100.0)	171 (100.0)	169 (100.0)	167 (100.0)	172 (100.0)	170 (100.0)	171 (100.0)	1360 (100.0)
Not prematurely discontinued trial medication	161 (94.7)	153 (90.0)	154 (90.1)	156 (92.3)	150 (89.8)	160 (93.0)	150 (88.2)	151 (88.3)	1235 (90.8)
Prematurely discontinued trial medication	9 (5.3)	17 (10.0)	17 (9.9)	13 (7.7)	17 (10.2)	12 (7.0)	20 (11.8)	20 (11.7)	125 (9.2)
Adverse event	6 (3.5)	5 (2.9)	4 (2.3)	3 (1.8)	4 (2.4)	3 (1.7)	6 (3.5)	5 (2.9)	36 (2.6)
Study disease worsening	0	0	0	0	0	0	1 (0.6)	0	1 (0.1)
Other pre-existing disease worsening	0	0	0	0	1 (0.6)	0	1 (0.6)	0	2 (0.1)
Other adverse event	6 (3.5)	5 (2.9)	4 (2.3)	3 (1.8)	3 (1.8)	3 (1.7)	4 (2.4)	5 (2.9)	33 (2.4)
Lack of efficacy[1]	0	0	0	0	0	0	1 (0.6)	0	1 (0.1)
Non-compliance with protocol	1 (0.6)	1 (0.6)	0	1 (0.6)	2 (1.2)	1 (0.6)	2 (1.2)	3 (1.8)	11 (0.8)
Lost to follow-up	0	6 (3.5)	7 (4.1)	2 (1.2)	3 (1.8)	4 (2.3)	3 (1.8)	2 (1.2)	27 (2.0)
Refused to continue trial medication	2 (1.2)	5 (2.9)	4 (2.3)	4 (2.4)	4 (2.4)	3 (1.7)	8 (4.7)	7 (4.1)	37 (2.7)
Other reason	0	0	2 (1.2)	3 (1.8)	4 (2.4)	1 (0.6)	0	3 (1.8)	13 (1.0)

[1] Includes patients who prematurely discontinued treatment due to a hyperglycaemic event and a blood glucose value above the protocol-defined level, despite administration of rescue medication.

Source: Table 10.1:3 1276.1 Study Report Body

There was a higher rate of premature discontinuations in the United States, Turkey, and France (all >15%) than in other countries.

In the open-label group, out of 53 treated patients, 49 patients (92.5%) completed the 24-week treatment period. Of the 4 patients (7.5%) who prematurely discontinued trial medication, 2 patients were lost to follow-up, 1 patient refused to continue trial medication (not due to an adverse event), and 1 patient discontinued due to reason 'other'.

Table 4 Number of Randomized Patients by Stratum- RS

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total number of patients	170 (100.0)	170 (100.0)	172 (100.0)	170 (100.0)	168 (100.0)	172 (100.0)	171 (100.0)	171 (100.0)
HbA_{1c} at screening [%]								
<8.5	66 (38.8)	67 (39.4)	67 (39.0)	65 (38.2)	64 (38.1)	66 (38.4)	65 (38.0)	66 (38.6)
≥8.5	104 (61.2)	103 (60.6)	105 (61.0)	106 (61.8)	104 (61.9)	106 (61.6)	106 (62.0)	105 (61.4)
eGFR (MDRD) [mL/min/1.73m^2]								
≥90	91 (53.5)	93 (54.7)	92 (53.5)	94 (55.3)	92 (54.8)	94 (54.7)	93 (54.4)	92 (53.8)
<90	79 (46.5)	77 (45.3)	80 (46.5)	76 (44.7)	76 (45.2)	78 (45.3)	78 (45.6)	79 (46.2)
Geographical region								
Latin America	47 (27.6)	47 (27.6)	48 (27.9)	47 (27.6)	48 (28.6)	48 (27.9)	47 (27.5)	47 (27.5)
Europe	45 (26.5)	46 (27.1)	47 (27.3)	48 (28.2)	46 (27.4)	47 (27.3)	47 (27.5)	48 (28.1)
Asia	45 (26.5)	44 (25.9)	44 (25.6)	43 (25.3)	43 (25.6)	46 (26.7)	44 (25.7)	44 (25.7)
North America	33 (19.4)	33 (19.4)	33 (19.2)	32 (18.8)	31 (18.5)	31 (18.0)	33 (19.3)	32 (18.7)

Source: Table 10.1:2 1276.1 Study Report Body

The treatment arms were balanced with respect to the screening HbA1c (<8.5%, ≥8.5%), screening renal function (assessed by eGFR; <90 mL/min/1.73m^2 and ≥90 mL/min/1.73m^2), and geographical region (Table 4).

Protocol violations

Overall, 11.4% of all randomized patients had protocol violations leading to exclusion from the PPS. The frequency was higher in the metformin 1000 mg bid group compared to the other treatment groups, mainly due to a higher proportion of patients who were non-compliant with the drug intake. 5.6% of the randomized patients had protocol violations not leading to exclusion from the PPS. The most frequent cause was 'uncontrolled FPG level'. Two patients were reported as taking the wrong study medication. Patient no. (b) (6) was assigned to the open-label treatment group and should therefore have been treated with E12.5+M1000 bid. However, at the randomization visit, the patient received E5+M1000 bid and continued to take the incorrect medication for 1.5 months. The patient was analyzed based on assigned treatment (i.e. open-label E12.5+M1000 bid). The second patient reported to have taken the wrong study medication was patient no. (b) (6) who was randomized to treatment with M1000 bid but received E10 qd at Visit 5. The incorrect medication was taken for 6.4 weeks, and the patient was excluded from the PPS.

Table 5 Number of Patients with Important Protocol Violations Leading to Exclusion from the PPS with a Frequency of 1% or More in any Treatment Group – RS

	E12.5+M1000 bid N (%)	E12.5+M500 bid N (%)	E5+M1000 bid N (%)	E5+M500 bid N (%)	E25 qd N (%)	E10 qd N (%)	M1000 bid N (%)	M500 bid N (%)	Total N (%)
Randomised patients	170 (100.0)	170 (100.0)	172 (100.0)	170 (100.0)	168 (100.0)	172 (100.0)	171 (100.0)	171 (100.0)	1364 (100.0)
Patients with important protocol violation	27 (15.9)	27 (15.9)	28 (16.3)	25 (14.7)	28 (16.7)	23 (13.4)	35 (20.5)	23 (13.5)	216 (15.8)
Not leading to exclusion from PPS	11 (6.5)	4 (2.4)	10 (5.8)	8 (4.7)	15 (8.9)	12 (7.0)	9 (5.3)	7 (4.1)	76 (5.6)
Leading to exclusion from PPS	17 (10.0)	24 (14.1)	19 (11.0)	17 (10.0)	16 (9.5)	14 (8.1)	29 (17.0)	19 (11.1)	155 (11.4)
Non-compliance with drug intake[1]	12 (7.1)	18 (10.6)	9 (5.2)	11 (6.5)	10 (6.0)	10 (5.8)	23 (13.5)	16 (9.4)	109 (8.0)
Renal insufficiency or impairment[2]	2 (1.2)	2 (1.2)	4 (2.3)	2 (1.2)	2 (1.2)	1 (0.6)	4 (2.3)	0	17 (1.2)
HbA_{1c} out of range[3]	1 (0.6)	1 (0.6)	2 (1.2)	1 (0.6)	1 (0.6)	3 (1.7)	1 (0.6)	0	10 (0.7)
No type 2 diabetes	0	0	0	0	0	0	2 (1.2)	0	2 (0.1)

[1] Overall study treatment compliance outside 80% and 120% or study treatment compliance below 80% in the last visit interval before the primary endpoint assessment
[2] As assessed by eCcr values at screening
[3] Before protocol amendment 1, the eligible HbA_{1c} range for randomised treatment was ≥7.0% and ≤10.0%. After protocol amendment 1, the eligible HbA_{1c} range for randomised treatment was ≥7.5% and ≤12.5%

Source: Table 10.3:1 1276.1 Study report body

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy assessment was the change in HbA1c from baseline to endpoint after 24 weeks of treatment. Baseline was defined as the last observation prior to the first intake of any randomized trial medication.

The treatment comparison of the adjusted mean change in HbA1c submitted by the Applicant in the FAS analysis set (OC) using an MMRM model is presented below in Table 6.

All treatment groups had reductions in HbA1c at 24 weeks. No clear dose dependence was observed between the E10 mg and E25 mg qd arms, or between E5+M500 bid and E12.5+M500. Similarly, no dose dependency was observed between the E5+M1000 bid and E12.5+M1000 bid groups. This is consistent with the original NDA review for empagliflozin, where dose dependency was not universally observed. The results of the confirmatory testing hierarchy comparing the combinations of empagliflozin and metformin with their individual components, and the subsequent comparisons of empagliflozin with metformin are outlined below.

Comparison of E12.5+M1000 bid with M1000 bid and with E25 qd (first and second steps of the confirmatory hierarchy)

The adjusted mean HbA1c reduction at 24 weeks in the E12.5+M1000 bid arm (-2.08%) was superior to the M1000 bid arm (-1.75%) with an adjusted mean treatment difference of -0.33% (95% CI: -0.56, -0.10). In the second step of the testing strategy, the E12.5+M1000 bid arm showed superiority to the E25 treatment arm with an adjusted mean treatment difference of -0.72% (95% CI: -0.95, -0.48).

Comparison of E12.5+M500 bid with M500 bid and with E25 qd (third and fourth steps of the confirmatory hierarchy)

After 24 weeks of treatment, the E12.5+M500 bid group had an adjusted mean HbA1c reduction of -1.93%, which was superior to the M500 bid group (mean treatment difference of -0.75% (95% CI: -0.98, -0.51)), and to the E25 qd with an adjusted mean treatment difference of -0.57% (95% CI: -0.81, -0.34).

Comparison of E5+M1000 bid with M1000 bid and with E10 qd (fifth and sixth steps of the confirmatory hierarchy)

The E5+M1000 bid (-2.07% HbA1c reduction at 24 weeks) showed superiority to the M1000 bid group (adjusted mean treatment difference of -0.33% (95% CI: -0.56, -0.09)), and to the E10 qd, with an adjusted mean treatment difference of -0.72% (95% CI: -0.95, -0.49).

Comparison of E5+M500 bid with M500 bid and with E10 qd (seventh and eighth steps of the confirmatory hierarchy)

The E5+M500 bid (-1.98% HbA1c reduction) showed superiority to the M500 bid group (adjusted mean treatment difference of -0.79% (95% CI: -1.03, -0.56)), and to the E10 qd, with an adjusted mean treatment difference of -0.63% (95% CI: -0.86, -0.40).

After comparing for superiority of the combination arms to the monotherapy arms, the testing hierarchy proceeded to compare monotherapy arms for non-inferiority.

Comparison of E25 qd with M1000 bid and E10 qd with M1000 bid (ninth and tenth steps of the confirmatory hierarchy)

Both empagliflozin doses failed to show non-inferiority to M1000 bid. For E25 qd, the adjusted mean treatment difference to M1000 bid was 0.39% (95% CI: 0.15, 0.62). For E10 qd, the adjusted mean treatment difference to M1000 bid was 0.40% (95% CI: 0.16, 0.63).

Sensitivity analyses reported by the Applicant showed similar results. It is notable that, in the comparisons involving M1000 BID, although the empagliflozin-metformin combinations were statistically superior, the numerical difference was small, and the upper bound of the 95% CI was close to 0 in both comparisons. This relationship is further explored in subpopulation analyses in section 5.1.7. The reason for the small difference in the effect size could potentially be explained by the choice of the study population, as in the treatment naïve and relatively recently diagnosed metformin monotherapy is usually very efficacious.

Table 6 Change from Baseline in HbA1c (%) at Week 24 – FAS (OC)

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Number of patients in analysis set	169	165	167	161	164	169	164	168
Baseline								
Mean baseline HbA_{1c} (SE)	8.66 (0.09)	8.84 (0.10)	8.65 (0.10)	8.68 (0.10)	8.86 (0.10)	8.62 (0.10)	8.55 (0.09)	8.69 (0.08)
Week 24								
Number of analysed patients	159	149	151	153	143	156	146	142
Mean HbA_{1c} (SE)	6.56 (0.08)	6.84 (0.09)	6.49 (0.08)	6.67 (0.07)	7.30 (0.09)	7.18 (0.09)	6.72 (0.08)	7.35 (0.11)
Change from baseline								
Mean (SE)	-2.12 (0.09)	-1.99 (0.11)	-2.12 (0.09)	-2.01 (0.09)	-1.48 (0.10)	-1.35 (0.09)	-1.81 (0.10)	-1.30 (0.09)
Adjusted[1] mean (SE)	-2.08 (0.08)	-1.93 (0.08)	-2.07 (0.08)	-1.98 (0.08)	-1.36 (0.08)	-1.35 (0.08)	-1.75 (0.09)	-1.18 (0.08)
Comparison vs. M1000 bid								
Adjusted[1] mean (SE)	-0.33 (0.12)	-	-0.33 (0.12)	-	0.39 (0.12)	0.40 (0.12)	-	-
95% CI	(-0.56, -0.10)	-	(-0.56, -0.09)	-	(0.15, 0.62)	(0.16, 0.63)	-	-
p-value non-inferiority[2]					0.6246	0.6558		
p-value superiority	0.0056	-	0.0062	-	-	-	-	-
Comparison vs. E25 qd								
Adjusted[1] mean (SE)	-0.72 (0.12)	-0.57 (0.12)	-	-	-	-	-	-
95% CI	(-0.95, -0.48)	(-0.81, -0.34)	-	-	-	-	-	-
p-value superiority	<0.0001	<0.0001	-	-	-	-	-	-
Comparison vs. M500 bid								
Adjusted[1] mean (SE)	-	-0.75 (0.12)	-	-0.79 (0.12)	-	-	-	-
95% CI	-	(-0.98, -0.51)	-	(-1.03, -0.56)	-	-	-	-
p-value superiority	-	<0.0001	-	<0.0001	-	-	-	-
Comparison vs. E10 qd								
Adjusted[1] mean (SE)	-	-	-0.72 (0.12)	-0.63 (0.12)	-	-	-	-
95% CI	-	-	(-0.95, -0.49)	(-0.86, -0.40)	-	-	-	-
p-value superiority	-	-	<0.0001	<0.0001	-	-	-	-

SE = standard error; CI = confidence interval

[1] The MMRM model includes baseline HbA_{1c} as linear covariate and baseline eGFR (MDRD), geographical region, treatment, visit, and visit-by-treatment interaction as fixed effects. The covariance used to fit the model was unstructured.
[2] One-sided test relative to a pre-specified margin of 0.35%

Source: Table 11.1.1.1:1 1276.1 Study Report Body

The FDA analysis of the primary endpoint using OC-IR imputation method are consistent with the analysis provided by the Applicant. For details, please see biometrics review by Dr. Sinks.

6.1.5 Analysis of Secondary Endpoints(s)

The two secondary endpoints that were predefined as key secondary endpoints and part of the planned hierarchical testing procedure are fasting plasma glucose, and body weight changes at 24 weeks. However, because the ninth step in the hierarchical testing strategy was not successful, both key secondary endpoint analyses should be considered exploratory.

Fasting plasma glucose

The Applicant reported that mean fasting plasma glucose levels at baseline were comparable between treatment groups.

Comparison of E12.5+M1000 bid with M1000 bid and with E25 qd

The mean adjusted FPG reduction at 24 weeks was -51 mg/dl in the E12.5+M1000 bid arm compared to -32.1 mg/dl in the M1000 mg arm (adjusted mean treatment difference of -18.8

mg/dL (95% CI: -25.5, -12.2; p<0.0001)), and -28 mg/dl in the E25 qd group (adjusted mean treatment difference of -23.0 mg/dL (95% CI: -29.7, -16.3; p<0.0001)).

Comparison of E12.5+M500 bid with M500 bid and with E25 qd

E12.5+M500 bid resulted in an adjusted mean change from baseline in FPG of -44 mg/dl compared to -17.2 mg/dl in the M500 bid arm (adjusted mean treatment difference of -26.7 mg/dL (95% CI: -33.5, -20.0; p<0.0001)), and -28 mg/dl in the E25 qd arm (-16.0 mg/dL (95% CI: -22.8, -9.2; p<0.0001)).

Comparison of E5+M1000 bid with M1000 bid and with E10 qd

The mean adjusted FPG reduction after 24 weeks was -47.8 mg/dl in the E5+M1000 bid arm compared to -32.1 mg/dl in the M1000 mg arm (adjusted mean treatment difference of -15.6 mg/dL (95% CI: -22.3, -8.9; p<0.0001)), and -32.9 mg/dl in the E10 qd group (adjusted mean treatment difference of -14.8 mg/dL (95% CI: -21.4, -8.2; p<0.0001)).

Comparison of E5+M500 bid with M500 bid and with E10 qd

The mean adjusted FPG reduction after 24 weeks was -45.5 mg/dl in the E5+M500 bid arm compared to -17.2 mg/dl in the M500 mg arm (adjusted mean treatment difference of -28.2 mg/dL (95% CI: -35.0, -21.5; p<0.0001)), and -32.9 mg/dl in the E10 qd group (adjusted mean treatment difference of -12.6 mg/dL (95% CI: -19.1, -6.0; p = 0.0002)).

All sensitivity analyses showed similar results.

Table 7 Change from Baseline in FPG [mg/dL] at Week 24 –FAS (OC)

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Number of patients in analysis set	169	165	167	161	164	169	164	168
Baseline								
Mean baseline FPG (SE)	167.9 (3.2)	171.2 (3.4)	163.7 (3.3)	165.9 (3.1)	176.9 (3.8)	170.0 (3.0)	169.0 (3.8)	172.6 (3.0)
Week 24								
Number of analysed patients	158	146	146	153	139	154	145	139
Mean FPG (SE)	116.2 (2.6)	124.3 (2.6)	116.3 (2.1)	121.3 (1.9)	138.6 (3.1)	133.4 (2.0)	130.7 (2.4)	149.0 (3.1)
Change from baseline								
Mean (SE)	-51.9 (3.6)	-45.6 (3.7)	-47.6 (3.0)	-44.3 (2.8)	-34.0 (3.5)	-33.3 (2.6)	-33.2 (3.2)	-21.4 (3.4)
Adjusted [1] mean (SE)	-51.0 (2.4)	-44.0 (2.4)	-47.8 (2.4)	-45.5 (2.4)	-28.0 (2.5)	-32.9 (2.4)	-32.1 (2.4)	-17.2 (2.5)
Comparison vs. M1000 bid								
Adjusted[1] mean (SE)	-18.8 (3.4)	-	-15.6 (3.4)	-	-	-	-	-
95% CI	(-25.5, -12.2)	-	(-22.3, -8.9)	-	-	-	-	-
p-value[2]	<0.0001	-	<0.0001	-	-	-	-	-
Comparison vs. E25 qd								
Adjusted[1] mean (SE)	-23.0 (3.4)	-16.0 (3.4)	-	-	-	-	-	-
95% CI	(-29.7, -16.3)	(-22.8, -9.2)	-	-	-	-	-	-
p-value[2]	<0.0001	<0.0001	-	-	-	-	-	-
Comparison vs. M500 bid								
Adjusted[1] mean (SE)	-	-26.7 (3.4)	-	-28.2 (3.4)	-	-	-	-
95% CI	-	(-33.5, -20.0)	-	(-35.0, -21.5)	-	-	-	-
p-value[2]	-	<0.0001	-	<0.0001	-	-	-	-
Comparison vs. E10 qd								
Adjusted[1] mean (SE)	-	-	-14.8 (3.4)	-12.6 (3.4)	-	-	-	-
95% CI	-	-	(-21.4, -8.2)	(-19.1, -6.0)	-	-	-	-
p-value[2]	-	-	<0.0001	0.0002	-	-	-	-

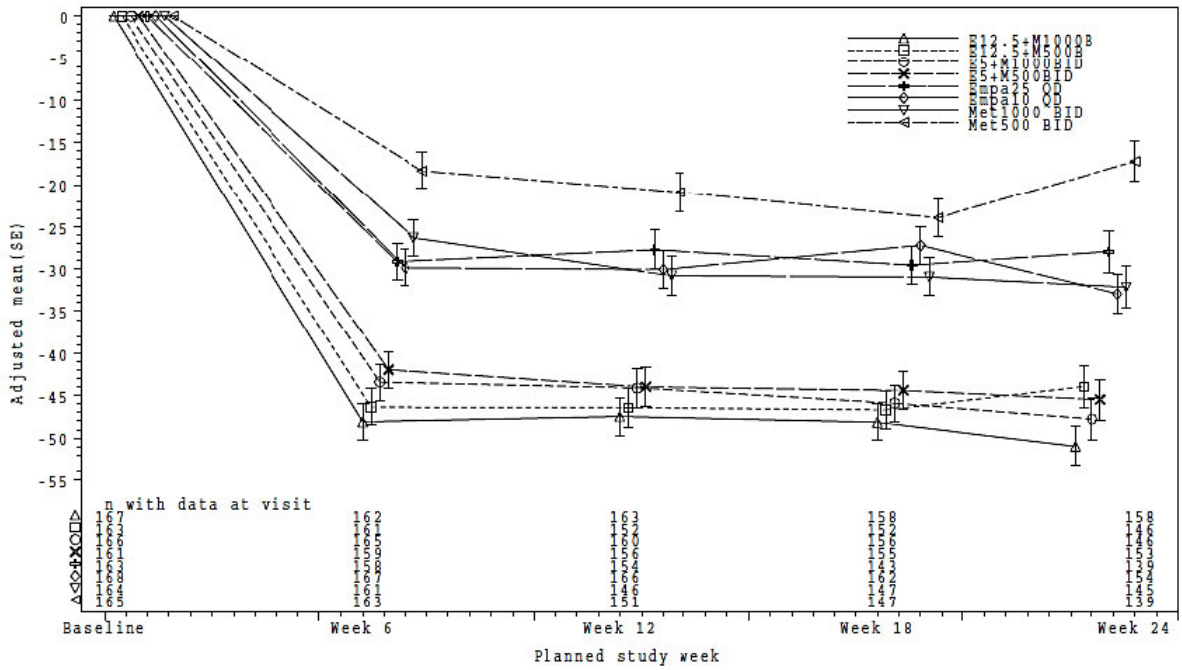
SE= standard error

[1] The MMRM model includes baseline FPG and baseline HbA_{1c} as linear covariates and baseline eGFR (MDRD), geographical region, treatment, visit, and visit-by-treatment interaction as fixed effects. The covariance used to fit the model was unstructured.
[2] Analysed in an exploratory manner

Source: Table 11.1.2.1:1 1276.1 Study Report Body

In all treatment groups, most changes in FPG occurred in the first 6 weeks of treatment (Figure 2), and were maintained for the remaining 18 weeks. The changes are consistent with the findings observed for HbA1c.

Figure 2 Adjusted Mean Changes from Baseline in FPG (mg/dl) Over Time – FAS (OC)



Source: Figure 11.1.2.1:1 1276.1 Study report body

Body weight

The changes in body weight from baseline to 24 weeks are presented in Table 9 below.

Comparison of E12.5+M1000 bid with M1000 bid

The reduction in body weight in the combination arm was -3.78 kg at 24 weeks, which was greater than the change in body weight seen with M1000 bid (-1.27 kg, mean adjusted treatment difference of -2.5 kg (95% CI: -3.33, -1.68; p<0.0001).

Comparison of E12.5+M500 bid with M500 bid

The reduction in body weight in the combination arm was -3.04 kg at 24 weeks, which was greater than the change in body weight seen with M500 bid (-0.52 kg, mean adjusted treatment difference of -2.52 kg (95% CI: -3.35, -1.69; p<0.0001).

Comparison of E5+M1000 bid with M1000 bid

The reduction in body weight in the combination arm was -3.48 kg at 24 weeks, which was greater than the change in body weight seen with M1000 bid (-1.27 kg, mean adjusted treatment difference of -2.20 kg (95% CI: -3.03, -1.37; p<0.0001).

Comparison of E5+M500 bid with M500 bid

The reduction in body weight in the combination arm was -2.77 kg at 24 weeks, which was greater than the change in body weight seen with M500 bid (-0.52 kg, mean adjusted treatment difference of -2.26 kg (95% CI: -3.09, -1.43; p<0.0001).

Table 8 Change from Baseline in Body Weight [kg] at Week 24 –FAS (OC)

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Number of patients in analysis set	169	165	167	161	164	169	164	168
Baseline								
Mean baseline weight (SE)	83.70 (1.54)	82.87 (1.45)	83.00 (1.49)	82.27 (1.51)	83.41 (1.59)	83.92 (1.53)	83.78 (1.57)	82.90 (1.65)
Week 24								
Number of analysed patients	160	149	150	155	143	155	148	140
Mean weight (SE)	79.99 (1.46)	79.71 (1.47)	78.58 (1.46)	79.35 (1.43)	81.48 (1.62)	82.19 (1.53)	81.62 (1.50)	82.67 (1.74)
Change from baseline								
Mean (SE)	-3.85 (0.31)	-3.03 (0.33)	-3.52 (0.33)	-2.75 (0.30)	-2.53 (0.36)	-2.46 (0.30)	-1.28 (0.33)	-0.57 (0.28)
Adjusted [1] mean (SE)	-3.78 (0.29)	-3.04 (0.30)	-3.48 (0.30)	-2.77 (0.30)	-2.38 (0.30)	-2.39 (0.29)	-1.27 (0.30)	-0.52 (0.30)
Comparison vs. M1000 bid								
Adjusted[1] mean (SE)	-2.50 (0.42)	-	-2.20 (0.42)	-	-	-	-	-
95% CI	(-3.33, -1.68)	-	(-3.03, -1.37)	-	-	-	-	-
p-value [2]	<0.0001	-	<0.0001	-	-	-	-	-
Comparison vs. M500 bid								
Adjusted [1] mean (SE)	-	-2.52 (0.42)	-	-2.26 (0.42)	-	-	-	-
95% CI	-	(-3.35, -1.69)	-	(-3.09, -1.43)	-	-	-	-
p-value [2]	-	<0.0001	-	<0.0001	-	-	-	-

SE= standard error

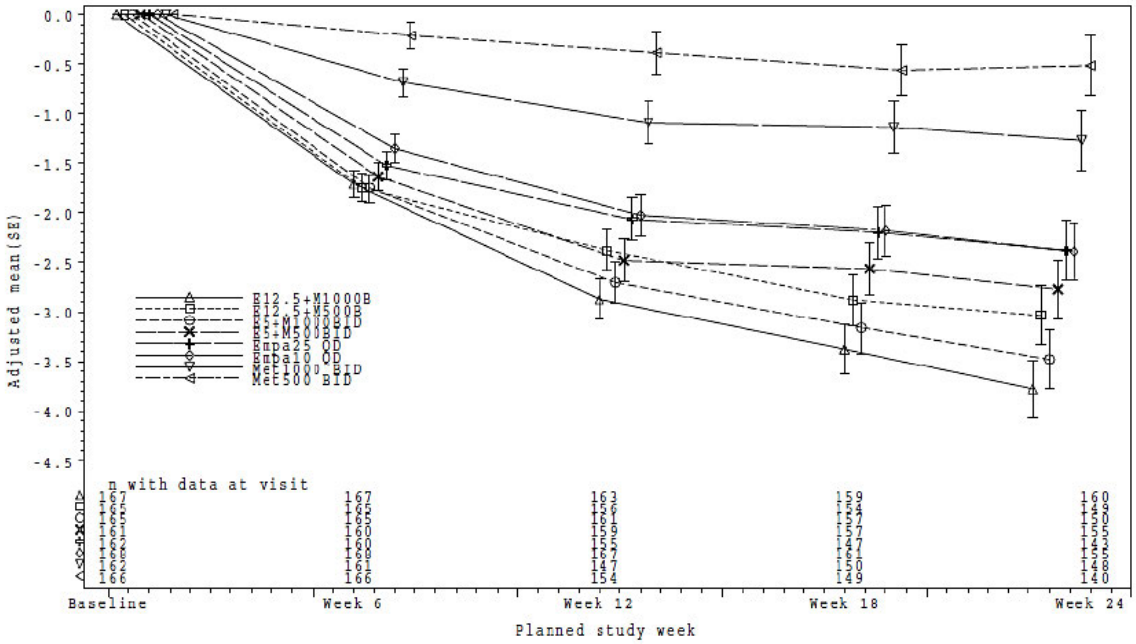
[1] The MMRM model includes baseline weight and baseline HbA_{1c} as linear covariates and baseline eGFR (MDRD), geographical region, treatment, visit, and visit-by-treatment interaction as fixed effects. The covariance used to fit the model was unstructured.
[2] Analysed in an exploratory manner

Source: Table 11.1.2.2:1 1276.1 Study report body

The differences between the combination treatment groups and the metformin monotherapy groups were apparent from week 6 and were sustained for the remainder of the study (Figure 3).

The Applicant submitted an analysis of the percentage change in body weight using MMRM on the FAS (OC) population. The percent reduction in body weight at Week 24was greater in the patients treated with the combination of empagliflozin and metformin (E12.5+M1000 bid: -4.33%; E12.5+M500 bid: -3.55%; E5+M1000 bid: -4.05%; E5+M500 bid: -3.10%) than in the patients treated with metformin monotherapy (M1000 bid: -1.21%; M500 bid: -0.40%).

Figure 3 Adjusted Mean Changes from Baseline in Body Weight (kg) Over Time – FAS (OC)



Source: Figure 11.1.2.2:1 1276.1 Study report body

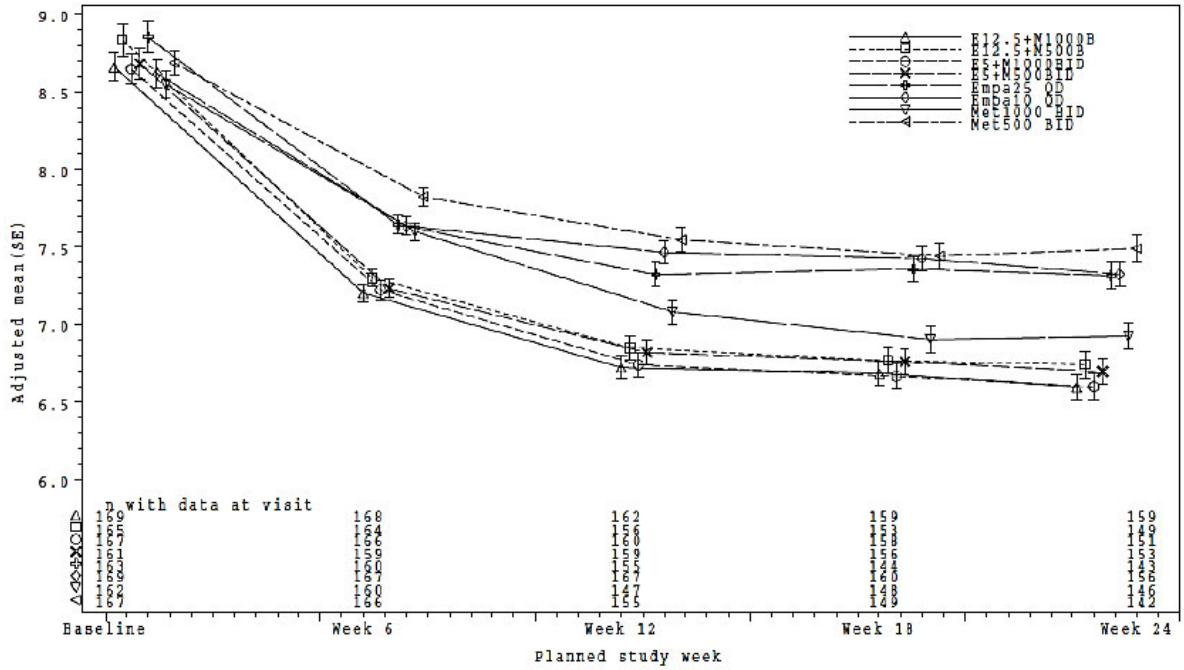
Reviewer Comment: The percent decrease in body weight is below the 5% standard for approval of medications for weight loss. In addition, it is possible that some of this effect isdue to the diuretic effect of empagliflozin, and therefore reversible once the empagliflozin is discontinued. The magnitude of change is in line with the current prescribing information for empagliflozin.

6.1.6 Other Endpoints

Change in HbA1c from baseline over time

As seen in Figure 4 below, most of the HbA1c changes in all treatment groups occurred in the first 12 weeks of treatment and were sustained for the remaining duration of the study.

Figure 4 Adjusted Mean HbA1c (%) Over Time – FAS (OC)



Source: Figure 11.1.1.2.2:1 1276.1 Study report body

Categorical HbA1c response

The Applicant defined categorical HbA1c responses as the proportion of patients reaching HbA1c levels of <7% after 24 weeks of treatment, and the proportion of patients attaining HbA1c lowering of 0.5% or more after 24 weeks of treatment. Overall, there were more patients in the E12.5+M1000 bid (69.2%), and E5+M1000 bid (70.1%) that achieved HbA1c <7% at the end of the 24 weeks compared to all other treatment arms. The same was true for the patients that started the study with a HbA1c ≥7%. The number and percentage of patients achieving this endpoint are shown in Table 10. Notably there were more patients who achieved HbA1C <7% after 24 weeks in the treatment groups containing empagliflozin 10 mg daily when compared to empagliflozin 25 mg daily.

Table 9 Number of Patients with Categorical Responses at Week 24 – FAS (NCF)

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Number of patients with HbA_{1c} <7.0% at Week 24, n^1/N^2 (%)								
Overall	117/169 (69.2)	96/165 (58.2)	117/167 (70.1)	103/161 (64.0)	57/164 (34.8)	78/169 (46.2)	97/164 (59.1)	65/168 (38.7)
Patients with baseline HbA_{1c} ≥7.0%	111/163 (68.1)	91/159 (57.2)	112/161 (69.6)	96/153 (62.7)	51/158 (32.3)	69/159 (43.4)	92/159 (57.9)	63/166 (38.0)
Number of patients with HbA_{1c} reduction from baseline ≥0.5% at Week 24, n (%)	149/169 (88.2)	136/165 (82.4)	146/167 (87.4)	145/161 (90.1)	116/164 (70.7)	127/169 (75.1)	132/164 (80.5)	114/168 (67.9)

[1] Responder patients
[2] Analysed patients

Source: Table 11.1.1.2.3:1 1276.1 Study report body

Reviewer comment: The combination treatment arms overall did better than the corresponding individual components in achieving HbA1c <7% at 24 weeks. Although the differences, at least when compared to M1000 bid group were small, these findings are supportive of the primary endpoint.

Blood pressure

Systolic blood pressure (SBP)

Small decreases in SBP were seen in thethe combination therapy groups and the empagliflozin only groups. In the combination therapy groups, the adjusted mean (SE) changes from baseline in SBP after 24 weeks were -3.24 mmHg (0.87) for E12.5+M1000 bid, -3.22 mmHg (0.90) for E12.5+M500 bid, -2.94 mmHg (0.90) for E5+M1000 bid, and -2.18 mmHg (0.89) for E5+M500 bid. For the patients treated with empagliflozin alone, the corresponding changes from baseline in SBP after 24 weeks were -2.35 mmHg (0.92) for E25 qd, and -2.15 mmHg (0.88) for E10 qd. For the patients treated with metformin alone, the changes were minimal: -0.18 mmHg (0.91) for M1000 bid and 0.78 mmHg (0.92) for M500 bid.

Diastolic blood pressure (DBP)

Small decreases in DBP were seen in thethe combination therapy groups and empagliflozin groups. In the combination therapy groups, the adjusted mean (SE) changes from baseline in DBP after 24 weeks were -1.89 mmHg (0.56) for E12.5+M1000 bid, -1.65 mmHg (0.58) for E12.5+M500 bid, -1.92 mmHg (0.58) for E5+M1000 bid, and -1.64 mmHg (0.57) for E5+M500 bid. For the patients treated with empagliflozin alone, the corresponding changes from baseline in DBP after 24 weeks were -0.95 mmHg (0.59) for E25 qd and -1.70 mmHg (0.57) for E10 qd. For the patients treated with metformin alone, the changes from baseline in DBP were -0.02 mmHg (0.58) for M1000 bid and 0.61 mmHg (0.59) for M500 bid.

Reviewer comment: The observed changes are small and are consistent with what has been observed in the empagliflozin development program. This could potentially be explained by the diuretic effect of empagliflozin. Although statistically significant, it is unclear whether the changes in SBP and DBP are clinically significant.

Composite endpoint

The Applicant submitted an analysis for a composite endpoint consisting of reduction in HbA1c by ≥0.5%, SBP by >3 mmHg, and body weight by >2%. The proportion of patients who fulfilled the composite endpoint was higher in the combination therapy groups compared to patients on either individual component.

Reviewer comment: Regardless of the differences reported by the Applicant, I do not believe that this composite endpoint has any clinical relevance.

Waist circumference

The Applicant reported that the changes in weight circumference were in line with the changes observed with body weight, which was expected.

Use of rescue medication

The Applicant stated that the use of rescue medication was originally designated as a safety endpoint, but was later changed to an efficacy endpoint. The proportions of patients requiring rescue medication was lower in each of the empagliflozin+metformin combination therapy groups compared to the groups of patients treated with the individual components. The most frequently introduced rescue medication was a sulphonylurea.

Table 10 Use of Rescue Medication – FAS (OR)

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25qd	E10qd	M1000 bid	M500 bid
Number of patients, N (%)	169 (100.0)	165 (100.0)	167 (100.0)	161 (100.0)	164 (100.0)	169 (100.0)	164 (100.0)	168 (100.0)
Number of patients with any rescue medication	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	6 (3.7)	3 (1.8)	7 (4.3)	9 (5.4)
With additional antidiabetic medication[1]								
Sulphonylurea	1 (0.6)	0	1 (0.6)	0	6 (3.7)	3 (1.8)	7 (4.3)	6 (3.6)
Insulin	1 (0.6)	0	0	0	0	0	0	3 (1.8)
Metformin	0	1 (0.6)	0	1 (0.6)	0	1 (0.6)	0	0
DPP-4 inhibitor	0	0	0	0	0	0	0	1 (0.6)
With premature discontinuation of trial medication due to lack of efficacy								
Start of additional antidiabetic medication on next day	0	0	0	0	0	0	1 (0.6)	0

[1] for 7 days or more or until treatment discontinuation

Source: Table 11.1.3.4:1 1276.1 Study Report Body

Patients in the open label group

At baseline, the mean (SD) HbA1c was 11.46% (1.57). After 24 weeks of treatment (based on OC imputation), there was a clinically meaningful reduction in HbA1c of -4.57% (SD 1.28). Baseline mean FPG (SD) was 262.35 mg/dL (73.50), and there was a reduction in FPG at 24 weeks of -134.91 mg/dL (SD 63.26). Mean weight at baseline (SD) was 93.69 kg (18.92), and a reduction was observed after 24 weeks of treatment of -2.96 kg (4.09).

6.1.7 Subpopulations

The Applicant performed subgroup analyses for the primary endpoint and key secondary endpoints on the FAS (OC) The following subgroups variables were investigated: baseline age, baseline HbA1c, geographical region, race, time since diagnosis of diabetes at baseline, and baseline renal function.

By age

The Applicant reported that the treatment effects in the subgroups by age are generally consistent with the findings in the overall population. The results are presented in Table 12 (4 age categories) and Table 13 (2 age categories) below. There were only 31 patients age 75 and above, and they were excluded from the analysis due to small numbers, therefore we cannot draw any meaningful efficacy conclusions in this age group. Comparison of the different treatment groups revealed that the change from baseline in HbA1c was only statistically significantly larger in the combination groups compared to metformin only groups in patients age 65 and below. In patients above the age of 65, the change in HbA1c in the combination groups was not statistically significantly different from the metformin only treatment groups. In the original empagliflozin NDA review, Dr. Chong noted that the efficacy of empagliflozin was reduced as age increased, possibly in part due to a decrease in renal function, which is common in this subpopulation. This is consistent with the Applicant's analysis for the currently reviewed study 1276.1. However, with the small number of patients above the age of 65 enrolled in this study, it is difficult to draw any meaningful conclusions regarding efficacy in this subgroup of patients, but the concern of reduced efficacy of empagliflozin (either alone or in combination) with increased age remains.

Table 11 HbA1c (%) Change from Baseline MMRM Results at Week 24 by Age (Years) (First Categorization – 4 Age Categories) − FAS (OC)

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+ M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+ M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Age group <50								
N	59	76	68	66	54	60	64	65
Mean baseline HbA1c (SE)	8.74 (1.19)	9.10 (1.36)	8.91 (1.22)	8.82 (1.31)	9.03 (1.38)	8.75 (1.18)	8.72 (1.06)	8.67 (1.00)
Change from baseline (SE)	-2.15 (1 36)	-2.25 (1.38)	-2.45 (1.11)	-2.08 (1.16)	-1.80 (1.10)	-1.39 (1 31)	-1.99 (1.35)	-1.01 (1.13)
Comparison vs M1000 bid								
Adjusted mean (SE)	-0.19 (0.18)		−0.34 (0.17)					
p-value	0.2907		0.0448					
Comparison vs M500 bid								
Adjusted mean (SE)		-1.10 (0.17)		−1.05 (0.16)				
p-value		<0.001		<0.0001				
Comparison vs E25 qd								
Adjusted mean (SE)	-0.47 (0.18)	-0.42 (0.18)						
p-value	0.0113	0.0172						
Comparison vs E10 qd								
Adjusted mean (SE)			−0.88 (0.17)	−0.65 (0.16)				
p-value			<0.0001	<0.0001				
Age group 50 to <65								
N	84	71	70	72	87	86	80	78
Mean baseline HbA1c (SE)	8.77 (1.04)	8.82 (1.26)	8.68 (1.29)	8.69 (1.13)	8.91 (1.27)	8.70 (1.29)	8.57 (1.20)	8.81 (1.07)
Change from baseline (SE)	-2.19 (1 01)	−1.87 (1.25)	−2.07 (1.16)	−2.06 (1.06)	−1.46 (1.35)	−1.42 (1.03)	−1.71 (1.22)	−1.54 (1.07)
Comparison vs M1000 bid								
Adjusted mean (SE)	-0.45 (0.15)		−0.33 (0.16)					
p-value	0.0036		0.0365					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.52 (0.16)		−0.65 (0.15)				
p-value		0.0015		<0.0001				
Comparison vs E25 qd								
Adjusted mean (SE)	-0.90 (0.15)	−0.60 (0.16)						
p-value	<0.0001	0.0002						
Comparison vs E10 qd								
Adjusted mean (SE)			−0.64 (0.15)	−0.62 (0.15)				
p-value			<0.0001	<0.0001				
Age group 65 to <75								
N	21	14	24	18	23	19	18	19
Mean baseline HbA1c (SE)	8.34 (1.32)	7.76 (0.70)	7.98 (0.77)	8.24 (1.41)	8.31 (1.04)	8.09 (1.05)	8.15 (1.12)	8.47 (1.08)
Change from baseline (SE)	−1.81(1.34)	−1.28 (0.62)	−1.45 (0.79)	−1.63 (1.10)	−0.91 (0.94)	−0.96 (0.74)	−1.67 (0.95)	−1.27 (1.12)
Comparison vs M1000 bid								
Adjusted mean	-0.06 (0 31)		0.02 (0.30)					

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+ M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
(SE)								
p-value	0.8532		0.9451					
Comparison vs M500 bid								
Adjusted mean		−0.31 (0.35)		−0.52 (0.30)				
(SE)								
p-value		0.3720		0.0835				
Comparison vs E25 qd								
Adjusted mean	-0.81 (0 30)	−0.54 (0.33)						
(SE)								
p-value	0.0063	0.1057						
Comparison vs E10 qd								
Adjusted mean			−0.62 (0.30)	−0.62 (0.30)				
(SE)								
p-value			0.0374	0.0396				
Age group 75 and above								
N	5	4	5	5	0	4	2	6
Mean baseline HbA1c (SE)	7.38 (0.52)	7.93 (0.29)	7.88 (0.99)	8.42 (1.75)		7.40 (0.67)	8.30 (0.14)	8.00 (0.81)
Change from baseline (SE)	−1.43 (0.45)	−1.20 (0.46)	−1.78 (0.95)	−1.72 (1.53)		−1.15 (1.03)	−1.25 (0.21)	−1.48 (1.22)

Source: Table 15.2.1.2.4.1:1 and 15.2.1.2.4.1:2 1276.1 Study report body

Table 12 HbA1c (%) Change from Baseline MMRM Results at Week 24 by Age (Years) (Second Categorization – 2 Age Categories) − FAS (OC)

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Age group <65								
N	143	147	138	138	141	146	144	143
Mean baseline HbA1c (SE)	8.76 (1.10)	8.96 (1.32)	8.79 (1.26)	8.75 (1.22)	8.94 (1.31)	8.72 (1.24)	8.61 (1.14)	8.75 (1.04)
Change from baseline (SE)	-2.17 (1.17)	-2.07 (1.33)	-2.26 (1.15)	-2.07 (1.11)	-1.58 (1.27)	-1.41 (1.15)	-1.84 (1.28)	-1.29 (1.12)
Comparison vs M1000 bid								
Adjusted mean	−0.37 (0.13)		−0.38 (0.13)					
(SE)								
p-value	0.0062		0.0036					
Comparison vs M500 bid								
Adjusted mean		−0.87 (0.14)		−0.85 (0.12)				
(SE)								
p-value		<0.0001		<0.0001				
Comparison vs E25 qd								
Adjusted mean	−0.72 (0.13)	−0.60 (0.14)						
(SE)								
p-value	<0.0001	<0.0001						
Comparison vs E10 qd								
Adjusted mean			−0.76 (0.13)	−0.64 (0.12)				
(SE)								
p-value			<0.0001	<0.0001				

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
≥65								
N	26	18	29	23	23	23	19	25
Mean baseline HbA1c (SE)	8.15 (1.26)	7.80 (0.63)	7.97 (0.69)	8.28 (1.45)	8.31 (1.04)	7.97 (1.02)	8.17 (1.06)	8.36 (1.02)
Change from baseline (SE)	-1.75 (1.25)	-1.26 (0.58)	-1.51 (0 81)	-1.65 (1.17)	-0.91 (0.94)	-1.00 (0.78)	-1.63 (0.91)	-1.33 (1.12)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.15 (0.34)		−0.07 (0.31)					
p-value	0.6682		0.8132					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.02 (0.37)		−0.43 (0.30)				
p-value		0.9605		0.1448				
Comparison vs E25 qd								
Adjusted mean (SE)	−0.79 (0.33)	−0.28 (0.38)						
p-value	0.0180	0.4579						
Comparison vs E10 qd								
Adjusted mean (SE)			−0.60 (0.30)	−0.59 (0.30)				
p-value			0.0453	0.0522				

Source: Table 15.2.1.2.4.1:3 and 15.2.1.2.4.1:4 1276.1 Study report body

By baseline HbA1c

The Applicant defined 2 version of subgroups relying on baseline HbA1c (version 1: <8.5% and ≥8.5%; version 2: <8.0%, 8.0 to <9.0%, 9.0 to <10.0%, and ≥10.0%).

Version 1

The E12.5+M1000 bid lowered HbA1c statistically significantly more than the respective doses of individual components for patients with baseline HbA1c <8.5%, while for the patients with baseline HbA1c >8.5%, the combination resulted in a HbA1c lowering similar to the M1000 bid group. Similarly, the E5+M1000 bid lowered HbA1c statistically significantly more than the respective doses of individual components for patients with baseline HbA1c <8.5%, while for the patients with baseline HbA1c >8.5%, the combination resulted in a HbA1c lowering similar to the M1000 bid group.

The E12.5+M500 bid lowered HbA1c statistically significantly more than the E25 qd individual component for patients with baseline HbA1c <8.5%, but was not different when compared to M500 bid, while for the patients with baseline HbA1c >8.5%, the combination resulted in a HbA1c lowering that was statistically larger than any of the respective dose of the individual

components. The E5+M500 bid lowered HbA1c similar to the respective doses of individual components for patients with baseline HbA1c <8.5%, while for the patients with baseline HbA1c >8.5%, the combination resulted in a HbA1c lowering that was statistically larger than any of the respective dose of the individual components.

In conclusion, for patients with HbA1c at baseline <8.5%, the difference between the metformin monotherapy groups and the corresponding combination therapy groups was minimal, while for patients with baseline HbA1c ≥8.5%, no benefit was seen when adding any dose of empagliflozin to M1000 bid. This may suggest that, for the patient population selected for this study (treatment naïve, relatively recently diagnosed with T2DM, mostly with normal renal function), if the baseline HbA1c is <8.5%, then metformin alone may be sufficient. For the subgroup of patients with baseline HbA1c >8.5%, one could conclude that a subtherapeutic dose of metformin (1000 mg daily) is not as good in lowering HbA1c as the corresponding combination therapy with either empagliflozin dose, while a therapeutic dose of metformin (2000 mg daily) results in HbA1c reduction at 24 weeks that is similar to the corresponding combination treatment groups. Because of the small subgroup size, it is possible that the findings are due to chance, and it is not clear that such conclusions would be reproducible on a larger sample size.

Table 13 Change from Baseline in HbA1c [%] at Week 24 by Baseline HbA1c Category –FAS (OC)

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
HbA1c group								
<8.5%								
N	85	75	80	74	69	85	86	77
Mean baseline HbA1c (SE)	7.75 (0.05)	7.68 (0.05)	7.62 (0.05)	7.60 (0.06)	7.64 (0.06)	7.62 (0.06)	7.70 (0.05)	7.80 (0.05)
Change from baseline (SE)	-1.53 (0.09)	-1.30 (0.08)	-1.48 (0.08)	-1.15 (0.08)	-0.85 (0.10)	-0.92 (0.08)	-1.18 (0.09)	-1.06 (0.09)
Comparison vs M1000 bid								
Adjusted mean (SE)	-0.37 (0.18)		-0.34 (0.17)					
p-value	0.0363		0.0443					
Comparison vs M500 bid								
Adjusted mean (SE)		-0.24 (0.20)		-0.12 (0.17)				
p-value		0.2164		0.4834				
Comparison vs E25 qd								
Adjusted mean (SE)	-0.65 (0.19)	-0.40 (0.20)						
p-value	0.0007	0.0474						
Comparison vs E10 qd								
Adjusted mean (SE)			-0.55 (0.17)	-0.22 (0.16)				

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
p-value			0.0011	0.1658				
≥8.5%								
N	84	90	87	87	94	84	76	90
Mean baseline HbA1c (SE)	9.59 (0.09)	9.80 (0.10)	9.60 (0.10)	9.60 (0.10)	9.75 (0.09)	9.63 (0.09)	9.52 (0.10)	9.45 (0.08)
Change from baseline (SE)	-2.71 (0.14)	-2.57 (0.16)	-2.74 (0.13)	-2.71 (0.10)	-1.97 (0.15)	-1.86 (0.15)	-2.53 (0.15)	-1.53 (0.16)
Comparison vs M1000 bid								
Adjusted mean (SE)	-0.28 (0.19)		-0.24 (0.17)					
p-value	0.1254		0.1599					
Comparison vs M500 bid								
Adjusted mean (SE)		-1.26 (0.18)		-1.35 (0.16)				
p-value		<0.0001		<0.0001				
Comparison vs E25 qd								
Adjusted mean (SE)	-0.83 (0.18)	-0.76 (0.18)						
p-value	<0.0001	<0.0001						
Comparison vs E10 qd								
Adjusted mean (SE)			-0.88 (0.17)	-0.93 (0.16)				
p-value			<0.0001	<0.0001				

Source: Table 11.1.1.3:1 1276.1 Study Report Body

Version 2

The E12.5+M1000 bid, the HbA1c lowering was only statistically significantly better when compared to E25 qd in the patients with HbA1c 8% and above, while it was not statistically different compared to the M1000 bid arm in any of the HbA1c subgroups.

For the E12.5+M500 bid, the HbA1c lowering was only statistically significantly better when compared to E25 qd in the patients with HbA1c 9% and above, while there was a statistically significant difference compared to the M500 bid arm in patients with baseline HbA1c 8% and above.

The E5+M1000 bid, the HbA1c lowering was statistically significantly better when compared to E25 qd in all baseline HbA1c subgroups, while compared to the M1000 bid arm the combination therapy was only statistically better in the patients with baseline HbA1c 8 to <9%.

The E5+M500 bid, the HbA1c lowering was statistically significantly better when compared to the individual components in patients with HbA1c 8% and above, but not in patients with baseline HbA1c <8%.

Reviewer comment: It appears that M1000 bid performed very similar to the combination for almost all HbA1c subgroups.

By race

The Applicant performed the subgroup analysis by race for the categories 'White', 'Black or African American', 'Asian', and 'Other'.

In the White patients, the E12.5+M1000 bid, E12.5+M500 bid, and E5+M500 bid treatment groups were statistically better compared to either corresponding monotherapy component in terms of mean HbA1c reduction at 24 weeks. The E5+M1000 bid group was not better when compared to the M1000 bid, but was better than E10 qd group.
In the Asian patients, the E12.5+M1000 bid was better than E 25 qd, but not better than M1000 bid monotherapy arm. Both E5+M1000 bid, and E5+M500 bid resulted in a statistically significant HbA1c reduction at 24 weeks compared to the corresponding individual components. The E12.5+M500 bid was better than M500 bid monotherapy, but not better than E25 qd monotherapy group.

In the Black or African American patients, the combination treatment groups did not result in a statistically significant difference in the adjusted mean change from baseline HbA1c when compared to either of the individual components treatment groups. However, due to small numbers (62 patients), I do not think that there is sufficient information to inform a conclusion in this racial group.

In the patients classified racially as Other, the combination treatment groups containing M1000 bid resulted in HbA1c reduction at 24 weeks that was no different than the M1000 bid monotherapy arm, but better than the corresponding empagliflozin monotherapy arms. The combination therapy arms containing M500 bid did better than either corresponding individual component.

By geographical region

The results by geographical region are presented in Table 14 below. Notably, regardless of the geographical region, the change in HbA1c at 24 weeks with E12.5+M1000 bid was no different than the change observed with M1000 bid alone. In Europe and Latin America, the same was true for the E5+M1000 bid, and M1000 bid groups. The combination groups containing M500 bid resulted in a decrease in HbA1c that was statistically better compared to the M500 bid alone group (except the E12.5+M500 bid in Europe).

Table 13 Change from Baseline in HbA1c by Geographical Region FAS-OC

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Europe								
N	45	44	46	47	44	47	47	47
Mean baseline HbA1c (SE)	8.12 (0.14)	8.21 (0.14)	8.13 (0.12)	8.12 (0.18)	8.25 (0.14)	7.97 (0.12)	8.18 (0.12)	8.38 (0.16)
Change from baseline (SE)	−1.78 (0.14)	−1.45 (0.15)	−1.71 (0.15)	−1.67 (0.17)	−1.10 (0.17)	−1.09 (0.12)	−1.63 (0.16)	−1.23 (0.16)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.26 (0.24)		−0.15 (0.22)					
p-value	0.2804		0.5097					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.31 (0.25)		−0.55 (0.21)				
p-value		0.2184		0.0094				
Comparison vs E25 qd								
Adjusted mean (SE)	−0.71 (0.24)	−0.35 (0.26)						
p-value	0.0032	0.1770						
Comparison vs E10 qd								
Adjusted mean (SE)			−0.53 (0.22)	−0.50 (0.21)				
p-value			0.0149	0.0182				
North America								
N	33	30	30	29	31	29	30	31
Mean baseline HbA1c (SE)	8.49 (0.20)	8.57 (0.22)	8.61 (0.24)	8.66 (0.23)	8.79 (0.25)	8.62 (0.23)	8.49 (0.22)	8.60 (0.18)
Change from baseline (SE)	−2.20 (0.19)	−2.20 (0.20)	−2.11 (0.21)	−1.87 (0.18)	−1.66 (0.21)	−1.52 (0.22)	−1.76 (0.20)	−1.41 (0.21)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.53 (0.29)		−0.58 (0.28)					
p-value	0.0732		0.0410					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.98 (0.31)		−0.58 (0.27)				
p-value		0.0018		0.0328				
Comparison vs E25 qd								
Adjusted mean (SE)	−0.67 (0.29)	−0.71 (0.31)						
p-value	0.0218	0.0238						
Comparison vs E10 qd								
Adjusted mean (SE)			−0.80 (0.28)	−0.40 (0.27)				
p-value			0.0044	0.1381				
Latin America								
N	47	47	47	43	47	48	45	47
Mean baseline	8.96 (0.17)	9.14 (0.20)	8.77 (0.18)	9.10 (0.19)	9.28 (0.19)	9.01 (0.18)	8.74 (0.19)	8.82 (0.15)

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
HbA1c (SE) Change from baseline (SE)	−2.42 (0.21)	−2.25 (0.20)	−2.29 (0.19)	−2.32 (0.19)	−1.60 (0.23)	−1.64 (0.20)	−2.08 (0.22)	−1.47 (0.19)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.27 (0.23)		−0.06 (0.22)					
p-value	0.2493		0.7842					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.87 (0.25)		−0.88 (0.22)				
p-value		0.0005		<0.0001				
Comparison vs E25 qd								
Adjusted mean (SE)	−0.99 (0.23)	−0.80 (0.25)						
p-value	<0.0001	0.0014						
Comparison vs E10 qd								
Adjusted mean (SE)			−0.58 (0.22)	−0.69 (0.22)				
p-value			0.0086	0.0016				
Asia								
N	44	44	44	42	42	45	42	43
Mean baseline HbA1c (SE)	9.03 (0.17)	9.32 (0.21)	9.10 (0.20)	8.90 (0.17)	9.07 (0.20)	8.88 (0.20)	8.82 (0.18)	8.95 (0.15)
Change from baseline (SE)	−2.07 (0.18)	−2.06 (0.25)	−2.42 (0.18)	−2.15 (0.16)	−1.65 (0.20)	−1.26 (0.17)	−1.72 (0.22)	−1.10 (0.20)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.33 (0.25)		−0.61 (0.23)					
p-value	0.1743		0.0089					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.99 (0.26)		−1.11 (0.23)				
p-value		0.0002		<0.0001				
Comparison vs E25 qd								
Adjusted mean (SE)	−0.51 (0.24)	−0.48 (0.26)						
p-value	0.0372	0.0645						
Comparison vs E10 qd								
Adjusted mean (SE)			−1.04 (0.22)	−0.87 (0.22)				
p-value			<0.0001	<0.0001				

Source: Modified from Table 15.2.1.2.4.5: 1 1276.1 Study report body

By renal function

Considering the mechanism of action of empagliflozin, its efficacy could conceivably be altered by renal impairment. To facilitate analysis of efficacy by baseline renal function, eGFR calculated by the Modification of Diet in Renal Disease (MDRD) formula was used to group patients. Normal renal function was defined as eGFR ≥ 90 ml/min/1.73 m2, mild renal

impairment was defined as 60 to < 90 ml/min/1.73 m^2. The Applicant reported that there were no patients with baseline eGFR < 60ml/min/1.73 m^2 at baseline in this study.

In patients with normal renal function, the empagliflozin-metformin combination therapy groups resulted in a decrease in HbA1c at 24 weeks that was statistically better than with the corresponding individual components. However, in patients with mild renal impairment, the M1000 bid group had a decrease in HbA1c at 24 weeks that was similar to what was observed in the combination therapy arms containing M1000 bid, which makes me question whether adding any dose of empagliflozin to M1000 bid has any benefit in this subpopulation.

Table 14 Change from Baseline in HbA1c by Baseline eGFR FAS-OC

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
eGFR ≥90 mL/min/1.73 m^2								
N	94	90	88	84	80	90	82	80
Mean baseline HbA1c (SE)	8.75 (0.12)	9.02 (0.14)	8.83 (0.13)	8.81 (0.14)	9.15 (0.16)	8.84 (0.13)	8.78 (0.13)	8.67 (0.12)
Change from baseline (SE)	−2.19 (0.13)	−2.13 (0.16)	−2.34 (0.13)	−2.01 (0.13)	−1.59 (0.16)	−1.49 (0.14)	−1.76 (0.16)	−1.22 (0.14)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.45 (0.17)		−0.56 (0.16)					
p-value	0.0102		0.0006					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.99 (0.19)		−0.83 (0.16)				
p-value		<0.0001		<0.0001				
Comparison vs E25 qd								
Adjusted mean (SE)	−0.77 (0.18)	−0.71 (0.19)						
p-value	<0.0001	0.0001						
Comparison vs E10 qd								
Adjusted mean (SE)			−0.82 (0.16)	−0.54 (0.16)				
p-value			<0.0001	0.0006				
eGFR 60 to <90 mL/min/1.73 m^2								
N	69	70	73	74	81	71	80	82
Mean baseline HbA1c (SE)	8.58 (0.13)	8.63 (0.15)	8.46 (0.14)	8.57 (0.14)	8.60 (0.13)	8.36 (0.15)	8.35 (0.12)	7.27 (0.14)
Change from baseline (SE)	−2.07 (0.14)	−1.79 (0.12)	−1.91 (0.13)	−2.02 (0.13)	−1.45 (0.13)	−1.15 (0.12)	−1.88 (0.13)	−1.39 (0.12)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.23 (0.19)		−0.11 (0.17)					
p-value	0.2132		0.5246					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.52 (0.20)		−0.77 (0.17)				

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
p-value		0.0076		<0.0001				
Comparison vs E25 qd								
Adjusted mean (SE)	−0.66 (0.19)	−0.37 (0.19)						
p-value	0.0004	0.0597						
Comparison vs E10 qd								
Adjusted mean (SE)			−0.73 (0.17)	−0.80 (0.17)				
p-value			<0.0001	<0.0001				

Source: Modified from Table 15.2.1.2.4.10:1 1276.1 Study report body

By time since the diagnosis of diabetes

In all treatment groups, more than 50% were relatively newly diagnosed (DM diagnosed ≤1 year). Only 62 patients in all treatment groups had T2DM for more than 10 years, therefore no meaningful conclusions can be drawn regarding this subgroup of patients. The results are presented in Table 16 below. It appears that the combination groups containing M1000 bid did not do better than the M1000 bid monotherapy group regardless of the duration of diabetes (except the E12.5+M1000 bid group in the patients with DM for > 1 to 5 years). In addition, in patients with DM for more than 5 years, there did not appear to be any benefit from adding empagliflozin 25 mg daily to either dose of metformin. However, the sample size is small in this subgroup, and it is not clear to what extent the results are generalizable.

Table 15 Change from Baseline in HbA1c by Time Since the Diagnosis of Diabetes FAS-OC

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Time since diagnosis								
≤1year								
N	98	87	98	95	90	82	90	101
Mean baseline HbA1c (SE)	8.77 (0.11)	8.93 (0.14)	8.66 (0.11)	8.61 (0.12)	8.82 (0.13)	8.70 (0.13)	8.58 (0.12)	8.75 (0.10)
Change from baseline (SE)	−2.17 (0.12)	−2.14 (0.14)	−2.28 (0.11)	−2.04 (0.12)	−1.66 (0.15)	−1.66 (0.12)	−1.95 (0.14)	−1.45 (0.13)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.16 (0.16)		−0.24 (0.15)					
p-value	0.3298		0.1063					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.71 (0.18)		−0.71 (0.14)				
p-value		<0.0001		<0.0001				
Comparison vs E25 qd								
Adjusted mean (SE)	−0.59 (0.17)	−0.50 (0.18)						
p-value	0.0004	0.0059						

	E12.5+ M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Comparison vs E10 qd								
Adjusted mean (SE)			−0.58 (0.15)	−0.41 (0.15)				
p-value			0.0002	0.0072				
> 1 to 5 years								
N	45	44	40	48	49	61	48	44
Mean baseline HbA1c (SE)	8.38 (0.18)	8.45 (0.17)	8.41 (0.21)	8.88 (0.22)	8.70 (0.18)	8.52 (0.16)	8.44 (0.17)	8.55 (0.16)
Change from baseline (SE)	−2.01 (0.17)	−1.69 (0.18)	−1.79 (0.17)	−2.00 (0.18)	−1.03 (0.15)	−1.07 (0.13)	−1.59 (0.19)	−1.09 (0.17)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.53 (0.24)		−0.28 (0.22)					
p-value	0.0253		0.2082					
Comparison vs M500 bid								
Adjusted mean (SE)		−0.77 (0.26)		−0.88 (0.21)				
p-value		0.0026		<0.0001				
Comparison vs E25 qd								
Adjusted mean (SE)	−1.12 (0.23)	−0.76 (0.25)						
p-value	<0.0001	0.0024						
Comparison vs E10 qd								
Adjusted mean (SE)			−0.69 (0.21)	−0.73 (0.19)				
p-value			0.0010	0.0002				
>5 to 10 years								
N	16	21	20	15	21	17	16	19
Mean baseline HbA1c (SE)	8.71 (0.23)	9.14 (0.33)	9.09 (0.33)	8.67 (0.28)	9.23 (0.31)	8.94 (0.32)	8.78 (0.26)	8.63 (0.26)
Change from baseline (SE)	−1.86 (0.42)	−2.00 (0.38)	−2.17 (0.40)	−1.86 (0.26)	−1.83 (0.25)	−0.98 (0.42)	−1.88 (0.40)	−1.08 (0.24)
Comparison vs M1000 bid								
Adjusted mean (SE)	−0.24 (0.43)		−0.50 (0.36)					
p-value	0.5675		0.1686					
Comparison vs M500 bid								
Adjusted mean (SE)		−1.01 (0.38)		−0.80 (0.35)				
p-value		0.0082		0.0234				
Comparison vs E25 qd								
Adjusted mean (SE)	−0.21 (0.39)	−0.50 (0.37)						
p-value	0.5975	0.1798						
Comparison vs E10 qd								
Adjusted mean (SE)			−1.15 (0.34)	−0.97 (0.36)				
p-value			0.0009	0.0077				
> 10 years								
N	10	13	9	3	4	9	10	4

Source: Modified from Table 15.2.1.2.4.19:1 1276.1 Study report body

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Empagliflozin is approved for use at 10 mg with a possibility of increasing to 25 mg daily if needed. In this efficacy supplement, the Applicant states that the relationship of drug dose or drug concentration to response was not investigated.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No changes.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The review of this efficacy supplement did not identify any new safety concerns. The safety findings are overall in line with the current prescribing information for empagliflozin and metformin.

Exposure was similar in the treatment groups, and dropouts and discontinuations were balanced between the treatment groups.

There were no deaths during the treatment period, but two deaths were reported in the post-study period. Evaluation of the very limited information provided for the two patients did not raise concerns that the deaths had any relationship to the study drug. Cardiovascular events were adjudicated by an independent cardiovascular event committee and no concerns were raised. There were no events of severe hypoglycemia, and only one event of documented symptomatic hypoglycemia with glucose concentration <54 mg/L. This is not surprising since these patients were not on insulin or sulfonylureas. No significant changes were observed in mean creatinine and mean eGFR after 24 weeks of treatment in either treatment group. Only three cases with renal dysfunction were identified as protocol-specified AEs, and one was particularly concerning – a 31 year old patient in the E5+M1000 bid group reported with a significant decrease in eGFR in the context of balanoposthitis, which is likely related to treatment of empagliflozin. Urinary tract infections were relatively balanced between treatment groups, no cases of urosepsis were reported. Three patients were reported with pyelonephritis events, all females: two events were reported as acute pyelonephritis (one in each E5+M1000 bid and E25 qd groups), and one with

chronic pancreatitis (M500 bid group). Genital infections were also balanced between treatment groups, but it is notable that, in the metformin monotherapy groups, there were no male patients with genital infections, while in most treatment groups containing empagliflozin there was an almost equal proportion of men and women with genital infections, including one case of phimosis in the E5+M1000 bid group. This information is already adequately captured in the prescribing information for empagliflozin.

There were no liver events or laboratory test abnormalities suggestive of drug-induced liver injury. Regarding fractures, 1-2 fractures/treatment group were reported for the combination therapy and empagliflozin monotherapy groups, while no fractures were reported for the metformin monotherapy groups. The number are small however, and could be due to chance.

No concern for an increase in the incidence of malignancies (generally or specifically for bladder cancer events) was identified in this study.

The risk for diabetic ketoacidosis was reviewed, and no cases of ketoacidosis were identified in this study.

7.1 Methods

Issues and concerns identified from the clinical study report safety section were addressed by the in-depth review of the narratives and datasets. JReview and MAED were used to confirm the Applicant's findings, for additional analyses, and for reviewer-generated tables.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Section 5.1 for a description of the clinical trial (1276.1) pertinent to this review. The safety review in this section addresses data from the 24 week study for the purpose of estimating incidences of adverse events and focuses on serious adverse events and unusual patterns or trends.

7.1.2 Categorization of Adverse Events

Preferred terms for adverse events were coded using MedDRA version 17.1.

For the analyses of AEs, all events with an onset after the first dose of randomized trial medication up to a period of 7 days after the last dose were assigned to the randomized treatment period. All AEs with onset before the first dose of randomized trial medication were assigned to 'pre-treatment' (screening or placebo run-in); all AEs with onset after the last dose+7 days were assigned to 'post-treatment'. If AEs were reported after a patient had completed the trial, these

events were assigned to the 'post-study' period. Treatment assignment for safety analyses in the randomized groups was ‘as first medication taken’.

Safety data were analyzed descriptively for all patients who took at least one dose of randomized trial medication (TS) or open-label medication (OLS). The Applicant presented the safety data by individual treatment group, and also pooled as follows: all empa (E10 qd and E25 qd), all met (M500 bid and M1000 bid), and all empa+met (E12.5+M1000 bid, E12.5+M500 bid, E5+M1000 bid, E5+M500 bid).

In the OL E12.5+M1000 bid group, the same concept regarding the treatment period was applied. For drug-related AEs in the OL group, patients who erroneously received wrong medication at the start of treatment were to be assigned to OL E12.5+M1000 bid treatment.

Reviewer comment: I compared a random selection of terms used by the investigator in describing an AE to the coded preferred term. AE events appear to have been appropriately classified.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Safety data were analyzed descriptively for all patients who took at least one dose of randomized trial medication (TS) or open-label medication (OLS).

Total exposure was also similar across randomized treatment groups, as were the mean and the median values of exposure duration (Table 17).

Table 16 Exposure to Study Drug – Treated Set

	E12.5+M1000 bid	E12.5+ M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Number of patients, N (%)	170 (100.0)	170 (100.0)	171 (100.0)	169 (100.0)	167 (100.0)	172 (100.0)	170 (100.0)	171 (100.0)
Exposure categories [weeks], N (%)								
>0 to 6	4 (2.4)	7 (4.1)	6 (3.5)	7 (4.1)	5 (3.0)	4 (2.3)	6 (3.5)	4 (2.3)
>6 to 12	3 (1.8)	4 (2.4)	2 (1.2)	2 (1.2)	4 (2.4)	3 (1.7)	7 (4.1)	5 (2.9)
>12 to 18	0	5 (2.9)	6 (3.5)	2 (1.2)	3 (1.8)	2 (1.2)	2 (1.2)	8 (4.7)
>18 to 24	72 (42.4)	81 (47.6)	82 (48.0)	72 (42.6)	85 (50.9)	74 (43.0)	83 (48.8)	79 (46.2)
>24	91 (53.5)	73 (42.9)	75 (43.9)	86 (50.9)	70 (41.9)	89 (51.7)	72 (42.4)	75 (43.9)
Exposure [days]								
Mean (SD)	165 (27.5)	160.2 (36.5)	160.3 (33.6)	161.9 (35.3)	162.2 (33.7)	163.6 (28.7)	159.0 (38.0)	160.1 (33.9)
Median	169.0	168.0	168.0	169.0	168.0	169.0	168.0	168.0
Range	(6, 197)	(1, 205)	(1, 188)	(1, 201)	(1, 230)	(3, 188)	(1, 227)	(1, 193)
Total exposure [years]	77.0	74.6	75.1	74.9	74.1	77.0	74.0	75.0

Source: Table 10.5:1 1276.1 Study Report Body

Treatment compliance was assessed at each visit based on tablet count of dispensed and returned medication. The Applicant reported that 94% of all patients were compliant within the accepted window of 80-120% and the distribution among treatment groups was comparable.

7.2.2 Explorations for Dose Response

There was no exploration of dose response in this study.

7.2.3 Special Animal and/or In Vitro Testing

No additional preclinical data were submitted for the purpose of this efficacy supplement.

7.2.4 Routine Clinical Testing

Routine testing that took place as part of the clinical study included measurement of vital signs (including weight), and laboratory testing (including measures of glycemic control, renal function, serum electrolytes, hematologic parameters, and liver enzymes).

7.2.5 Metabolic, Clearance, and Interaction Workup

No new information was submitted for this efficacy supplement.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

From the previous reviews of SGLT2 inhibitors, there are some identified potential adverse events. TheseThese include fractures, changes in plasma lipids, volume depletion events, decreased renal function, genitourinary infections, DILI, malignancies (specifically bladder), and incidence of early cardiovascular events (particularly stroke). In addition, diabetic ketoacidosis and urosepsis have emerged as a postmarketing concern in patients with type 2 diabetes treated with SGLT2 inhibitors and recently resulted in a safety labeling change issued on December 4, 2015.

7.3 Major Safety Results

7.3.1 Deaths

The Applicant reported that no patients died during the on-treatment phase of the study. One subject died in the post-study period, and one subject died without ever receiving study medication. No death was reported in the open label group.

- Patient no. (b) (6) in the E25 qd group is reported by the Applicant with PT “completed suicide” post-treatment (day 196, 25 days after the last dose of study drug).

- Patient no. (b) (6) was reported with PT atherosclerosis. However, patient no. (b) (6) did not enter the trial and therefore was not administered study medication, due to failure to meet the screening criteria.

Narratives were not submitted because the deaths did not happen during the study period. Even with the limited information available, I do not find these findings concerning that the deaths are related to the study drug.

7.3.2 Nonfatal Serious Adverse Events

The Applicant provided a listing with SAEs by treatment, primary system organ class and preferred term for the TS and case narratives. I generated a similar table using JReview and the datasets submitted by the Applicant (Table 18).

The SAE frequency was relatively low in all treatment groups, overall, 23 patients in the TS were reported with SAEs. The frequency of SAEs was higher in the E12.5 +M500 bid treatment arm compared to the other arms (6 patients, 3.5%). No SAE PT was reported in more than one patient.

Notably, there were no DKA events, or hypoglycemia SAEs, reported in either treatment group. Using JReview and the datasets provided by the Applicant (applying the safety population flag, on treatment+7 days flag, and serious AE flag), I generated the SAE table below. The table is similar with the information provided by the Applicant in Table 15.3.1.1: 7 of the study report body.

Table 17 Frequency of Patients with Serious Adverse Events by System Organ Class, Preferred Term and Treatment Arm

System Organ Class/ Preferred Term	E 12.5 + M1000 bid	E12.5 + M 500 bid	E 5 + M 1000 bid	E 5 + M500 bid	Empa 25 qd	Empa 10 qd	Met1000 bid	Met 500 bid
Total patients (%)	**171(100.0)**	**170(100.0)**	**171(100.0)**	**169(100.0)**	**167(100.0)**	**172(100.0)**	**169(100.0)**	**171(100.0)**
Patients with SAEs (%)	**2(1.2)**	**6(3.5)**	**3(1.8)**	**2(1.2)**	**3(1.8)**	**1(0.6)**	**3(1.8)**	**3(1.8)**
Blood and lymphatic system disorders								
Anemia	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Cardiac disorders								
Acute myocardial infarction	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	1(0.6)
Tachycardia paroxysmal	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Gastrointestinal disorders								
Pancreatitis acute	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
General disorders and administration site conditions								
Chest pain	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

System Organ Class/ Preferred Term	E 12.5 + M1000 bid	E12.5 + M 500 bid	E 5 + M 1000 bid	E 5 + M500 bid	Empa 25 qd	Empa 10 qd	Met1000 bid	Met 500 bid
Hepatobiliary disorders								
Bile duct stone	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Cholangitis acute	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Cholelithiasis	0(0.0)	1(0.6)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Hepatic cirrhosis	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Infections and infestations								
Appendicitis	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Dengue fever	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Herpes simplex encephalitis	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Nasal abscess	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Injury, poisoning and procedural complications								
Accidental overdose	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Rib fracture	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Metabolism and nutrition disorders								
Diabetes mellitus inadequate control	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Chronic lymphocytic leukemia	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Uterine leiomyoma	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Nervous system disorders								
Cerebral infarction	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Cerebrovascular accident	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
Renal and urinary disorders								
Hematuria	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Respiratory, thoracic and mediastinal disorders								
Chronic obstructive pulmonary disease	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Vascular disorders								
Hypertensive crisis	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
Peripheral arterial occlusive disease	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Peripheral ischemia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

In the OL group, 2 patients were reported with SAEs: patient no (b) (6) with hypomagnesemia, and patient no (b) (6) with acute myocardial infarction, unstable angina, and chest pain.

Reviewer comment: No DKA events were reported in the studied patient population, while post-marketing reports suggest an association between SGLT2 inhibitors, including empagliflozin, and ketoacidosis in both patients with type 1 and type 2 diabetes. This may be because the patients selected for this particular study are healthier and younger than the general population with type 2 diabetes, generally have good pancreatic reserve, and are less likely to have risk factors associated with ketoacidosis/DKA. In my view this study was not designed to capture such events and is not informative on this matter.

7.3.3 Dropouts and/or Discontinuations

The Applicant reported a similar incidence of premature discontinuation of study medication across treatment groups (Table 19): 6 patients in the E12.5+M1000 bid group (3.5%), 5 patients in the E12.5+M500 bid group (2.9%), 4 patients in the E5+M1000 bid group (2.3%), 3 patients in the E5+M500 bid group (1.8%), 4 patients in the E25 qd group (2.4%), 3 patients in the E10 qd group (1.7%), 6 patients in the M1000 bid group (3.6%), and 5 patients in the M500 bid group (2.9%). At the PT level, the only AE leading to premature discontinuation of the study medication reported more than once was diarrhea (2 events in each E12.5+M1000 bid, and E12.5+M500 bid, and M1000 bid group).

Hospitalization due to AE leading to discontinuation of the drug was reported in 1 patient in the E12.5+M500 bid (renal colic), 2 patients in the M1000 bid group (angina pectoris and diabetes mellitus inadequate control), and 1 patient in the M500 bid group (herpex simplex encephalitis).

Table 18 AEs Leading to Discontinuation by Treatment Group

System Organ Class/Preferred Term	E 12.5 + M1000 bid	E12.5 + M 500 bid	E 5 + M 1000 bid	E 5 + M500 bid	Empa 25 qd	Empa 10 qd	Met1000 bid	Met 500 bid
Total patients (%)	**171(100.0)**	**170(100.0)**	**171(100.0)**	**169(100.0)**	**167(100.0)**	**172(100.0)**	**169(100.0)**	**171(100.0)**
Patients with events (%)	**6(3.5)**	**5(2.9)**	**4(2.3)**	**3(1.8)**	**4(2.4)**	**3(1.7)**	**5(3.0)**	**5(2.9)**
Blood and lymphatic system disorders								
Anemia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Reticulocytosis	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Gastrointestinal disorders								
Constipation	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Diarrhea	2(1.2)	2(1.2)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	2(1.2)	1(0.6)
Gastritis	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Haemorrhoids	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Nausea	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
General disorders and administration site conditions								
Chest discomfort	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Drug intolerance	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Fatigue	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Infections and infestations								
Conjunctivitis	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Herpes simplex encephalitis	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Urinary tract infection	1(0.6)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	1(0.6)	1(0.6)	0(0.0)
Metabolism and nutrition disorders								
Diabetes mellitus inadequate control	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
Hyperuricemia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Musculoskeletal and connective tissue disorders								
Muscle spasms	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
Myalgia	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Neoplasms benign, malignant and unspecified(incl cysts and polyps)								
Chronic lymphocytic leukemia	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Nervous system disorders								
Dizziness	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Hypersomnia	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Tremor	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Psychiatric disorders								
Depression	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Renal and urinary disorders								
Azotaemia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Polyuria	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)

Renal injury	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Reproductive system and breast disorders								
Balanoposthitis	0(0.0)	1(0.6)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Pruritus genital	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Vulvovaginal pruritus	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Skin and subcutaneous tissue disorders								
Pain of skin	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Pruritus	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	1(0.6)	0(0.0)	0(0.0)
Rash pruritic	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

7.3.4 Significant Adverse Events

Prespecified significant adverse events included hepatic injury and decrease in renal function.

The criteria used to identify these events were:::

- Decreased renal function: creatinine ≥ 2x than the baseline value and >upper limit of normal (ULN);
- Hepatic injury defined by the following alterations of liver parameters after randomisation at Visit 3:
    - Elevation of AST and/or ALT ≥3xULN combined with an elevation of total bilirubin of ≥2xULN measured in the same blood draw sample;
    - Isolated elevation of AST and/or ALT ≥5xULN irrespective of any bilirubin elevation.

These significant adverse events are discussed further in section 7.3.5.

Other significant AEs were defined by the Applicant according to ICH E3. Adverse events categorized as other significant were non-serious AEs leading to premature discontinuation of study medication. The Applicant reported that, in the TS, there were 3 patients with events characterized as other significant in each of the E5+M500 bid and E10 qd groups, 4 patients in each E12.5+M500 bid, E5+M1000 bid, M1000 bid, and M500 bid groups, 5 patients in the E25 qd group, and 6 patients in the E12.5+M1000 bid group. No other significant AEs were reported in the OL group.

7.3.5 Submission Specific Primary Safety Concerns/Adverse Events of Special Interest

The following safety endpoints were defined for this trial:

- Adverse events (AEs);
- Hypoglycemic events;
- Cardiovascular events (CEC adjudication results);
- AEs of special interest (AESIs), including protocol-specified significant AEs that required expedited reporting to the sponsor by the investigator (decreased renal function, hepatic injury), hypoglycemic events (including confirmed investigator-defined hypoglycemic AEs), urinary tract infection (including acute pyelonephritis, sepsis, and asymptomatic bacteriuria), genital infection (including fungal balanitis and fungal vulvovaginitis), volume depletion, bone fracture, malignancies;
- Changes from baseline in vital signs;
- Changes from baseline in clinical laboratory values, including changes from baseline and percentage change from baseline in lipid profile parameters, including total cholesterol, HDL-cholesterol, LDL-cholesterol, LDL-cholesterol/HDL-cholesterol ratio, non-HDL-cholesterol, and triglycerides

Each of these will be discussed below:

Hypoglycemia

Every episode of plasma glucose ≤ 70 mg/dL (≤3.9 mmol/L) was to be documented in the eCRF with the respective time and date of occurrence. Any hypoglycemia with glucose values <54 mg/dL (<3.0 mmol/L), and all symptomatic and severe hypoglycemias were to be documented as hypoglycemic AE.

For the analyses, all hypoglycemic events were classified according to the following criteria:

- asymptomatic hypoglycemia: Event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L);
- documented symptomatic hypoglycemia with glucose concentration ≥54 mg/dL and ≤70 mg/dL (≥3.0 mmol/L and ≤3.9 mmol/L): Event accompanied by typical symptoms of hypoglycemia;
- documented symptomatic hypoglycemia with glucose concentration <54 mg/L (< 3.0 mmol/L): Event accompanied by typical symptoms of hypoglycemia but no need for external assistance;
- severe hypoglycemic episode: Event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

There were no events of severe hypoglycemia in any treatment group, which is not surprising considering the design of the study (patients with relatively recently diagnosed diabetes, not on insulin or sulfonylureas). The combination therapy treatment groups containing empagliflozin 12.5 mg bid had numerically slightly more hypoglycemia events compared to the other treatment groups, however, the numbers are small overall and I do not think that any conclusions regarding hypoglycemia are reasonable in this context.

Table 19 Frequency [N(%)] of Patients with Investigator Defined Asymptomatic or Symptomatic Hypoglycemia Reported as AE or non−AE by Treatment and Characteristics of Hypoglycemia −TS

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total patients (%)	170(100%)	170(100%)	171(100%)	169(100%)	167(100%)	172(100%)	170(100%)	171(100%)
Patients with hypoglycemia (%)	6 (3.5%)	5 (2.9%)	2 (1.2%)	4 (2.4%)	1 (0.6%)	2 (1.2%)	4 (2.4%)	2 (1.2%)
Severe hypoglycemia	0	0	0	0	0	0	0	0
Documented symptomatic hypoglycemia with glucose concentration <54 mg/L	0	1 (0.6%)	0	0	0	0	0	0
Documented symptomatic hypoglycemia with glucose concentration ≥54 mg/dL and ≤70 mg/dL	3 (1.8%)	1 (0.6%)	1 (0.6%)	0	1 (0.6%)	1 (0.6%)	2 (1.2%)	0
Asymptomatic hypoglycemia reported as AE	0	1 (0.6%)	0	0	0	0	0	0
Asymptomatic hypoglycemia not reported as AE	2 (1.2%)	1 (0.6%)	1 (0.6%)	4 (2.4%)	0	0	2 (1.2%)	2 (1.2%)
Symptomatic hypoglycemia and glucose concentration >70 mg/dl or not measured	1 (0.6%)	1 (0.6%)	0	0	0	1 (0.6%)	0	0

Source Modified using data from Table 15.3.1.3:3 1276.1 Study report body

No severe hypoglycemia was reported in the OL group. The Applicant reported one confirmed hypoglycemic event (1.9%), described as mild, with a plasma glucose between 54 and 70 mg/dl.

Cardiovascular Safety

An independent clinical event committee (CEC) was established for adjudication of potential cardiovascular endpoints. The CEC was composed of 10 members (5 cardiologists and 5 neurologists) and reviewed all reported fatal events, and any events suspected of stroke, transient ischemic attack (TIA), myocardial ischemia, hospitalization for unstable angina or heart failure, and stent thrombosis and revascularization procedures for this trial and for all phase III trials in the empagliflozin clinical development program, including, among others, empagliflozin monotherapy and empagliflozin+metformin therapy. The adjudication was performed without knowledge of the treatment assignment of any patient.

In the TS, the Applicant identified 17 patients that qualified for adjudication by the CEC: 1 patient (0.6%) in the E12.5+M500 bid dose group, 1 patient (0.6%) in the E12.5+M1000 bid dose group, 3 patients (1.8%) in the E5+M500 bid group, 3 patients (1.8%) in the E25 qd group, 3 patients (1.7%) in the E10 qd group, 4 patients (2.4%) in the M1000 bid group, and 2 patients (1.2%) in the M500 bid group. No patient had AEs that qualified for CEC-adjudication in the E5+M1000 bid treatment group.

Only two patients out of those with AEs sent for adjudication had AEs that were confirmed by the CEC as cardiovascular endpoints: 1 patient in the E12.5+M1000 bid group and 1 patient in the M1000 bid group. Each is briefly discussed below:

- Patient no (b) (6) a 61year old female assigned to E12.5+M1000 bid, was reported with SAE of infarctus cerebri that lead to hospitalization but not premature discontinuation of the study drug. The event occurred 3.5 weeks after beginning treatment with the study drug, and was assessed by the CEC as ischemic stroke; non-fatal neurological event; 3- and 4-MACE.
- Patient no (b) (6) a 53 year old female assigned to M1000 bid, was reported with left-sided weakness cerebrovascular accident that occurred approximately 5 months after commencing the study drug. The event was assessed by the CEC as ischemic stroke; non-fatal neurological event; 3- and 4-MACE, and did not lead to premature discontinuation of the study treatment.

In the OL group, 2 patients (3.8%) had AEs that qualified for CEC adjudication, only one was confirmed by the CEC.

- Patient no (b) (6) a 76 year old male, had an event adjudicated as acute myocardial infarction, unstable angina, coronary artery arteriosclerosis, and myocardial ischemia approximately 1.5 months after initiation of the study drug. He underwent cardiac

catheterization, which revealed 3 blockages, for which he underwent stents placement. The event did not lead to premature discontinuation of the study drug.

There was no apparent imbalance in adjudicated cardiovascular events in this study. Review of the submitted narratives does not raise any particular concerns that the events could be related to study medication. Nevertheless, is it inappropriate to draw any conclusions with regard to cardiovascular safety given that this trial had too few events. The cardiovascular safety of empagliflozin is being evaluated in dedicateddedicated cardiovascular outcomes trial, which is currently under review as a separate supplement.

Decreased renal function

The analysis of decreased renal function included review of adverse events reports, and review of laboratory data.

Decreased renal function (defined as increase in creatinine >2X from baseline and >ULN) was a protocol-specified AE and was to be reported by the investigators. The Applicant reported that 3 patients had renal AEs and renal laboratory findings, based on protocol-specified AEs and SMQ search categories (Table 21). None of the renal adverse events were reported as SAEs. One AE of azotemia in the metformin 500 mg bid group lead to treatment discontinuation. Brief narratives for the two patients are presented below.

- Patient no (b) (6) in the E12.5+M1000 bid treatment group: 43 year old Asian patient with T2DM for less than one year at study entry, developed what the Applicant reported as moderate decreased renal function on day 169 after randomization (one day after the last dose of trial medication). The patient's eGFR was 18 ml/min/1.73m^2 at the time of the event, from a pre-treatment value of 69 ml/min/1.73m^2. The narrative states that the patient was also being treated with amoxicillin and ambroxol for an upper respiratory tract infection at the time. Approximately one month after the event the eGFR was reported as back to baseline at 66 ml/min/1.73m$^{2.}$

Reviewer comment: This decrease in renal function couldcould be related to the study treatment in this case, most likely to the empagliflozin component. There is limited information on renal function after week 12. No additional measurements of renal function are reported from week 12 until the event.

- Patient no (b) (6) in the E5+M1000 bid group: 31 year old male from France with T2DM for less than one year at study entry, who developed balanoposthitis on day 62 since randomization, reported as resolved on day 108. Renal function was not reported at the time of this event. Subsequently, on day 141 after randomization, the patient was reported with PT blood creatinine increased. Per narrative, the eGFR decreased from 108 ml/min/1.73m^2 prior to starting the trial medication to 20 ml/min/1.73m^2 at the time of this event. The patient was off treatment as the study treatment was discontinued one day prior to the event due to the AE of balanoposthitis. Per SAE report, 2 days after the SAE was reported, the estimated glomerular filtration rate was 114 ml/hr.

Reviewer comment: While there is a lot of information missing in this case, this is a very significant decrease in renal function in a young patient with previously normal renal function in the context of balanoposthitis, and is concerning and likely attributable to the study drug. It is unclear if any intervention occurred from detection of decreased eGFR to resolution. Assuming no intervention, the rapid recovery could suggest resolution due to discontinuation of therapy or an error in laboratory test reporting. The available data are insufficient to draw any conclusions.

- Patient no (b) (6) in the M500 bid group: 52-year old Asian female known to have hadT2DM for >1 and ≤5 years at study entry, with a eGFR of 58 ml/min/1.73m^2 on the day of the treatment start, was reported with AE of azotemia on day 85 since randomization. (eGFR 39 ml/min/1.73m^2). There were a few other ongoing events at the time, such as vulvovaginal candidiasis, UTI, anemia, reticulocytosis, hyperuricemia. The study drug was discontinued on day 92 after randomization. Laboratory evaluation approximately one week after treatment discontinuation showed no real improvement in eGFR.

Reviewer comment: It is difficult to assess whether this event can be attributable to the study drug but this possibility cannot be excluded. However, this patient did have a relatively low eGFR even prior to starting the trial medication, putting her at increased risk of experiencing worsening renal function.

Table 20 Summary of Patients with Renal Adverse Events or Renal Laboratory Findings-Treated Set

Patient no.	Age [years]/ gender	AE (PT)	SAE	Intensity	Drug relation[2]	Discontinuation[3]	Start day[4]	Relevant laboratory finding[5]
Treatment at onset: E12.5+M1000 bid								
16464	43/F	Renal impairment[1]	No	Moderate	Yes	No	169	Yes
Treatment at onset: E5+M500 bid								
14221	31/M	Blood creatinine increased	No	Mild	No	No	141	Yes
Treatment at onset: M500 bid								
16451	52/F	Azotaemia	No	Moderate	No	Yes	85	No

[1]Included in SMQs 'acute renal failure'
[2]As judged by the investigator
[3]Leading to premature discontinuation of trial medication
[4]Relative to the start of the treatment period (first intake of trial medication)
[5]Increase of creatinine of ≥2-fold from baseline and creatinine >ULN

Source: Table 12.2.3.2:1 1276.1 study report body 1276.1

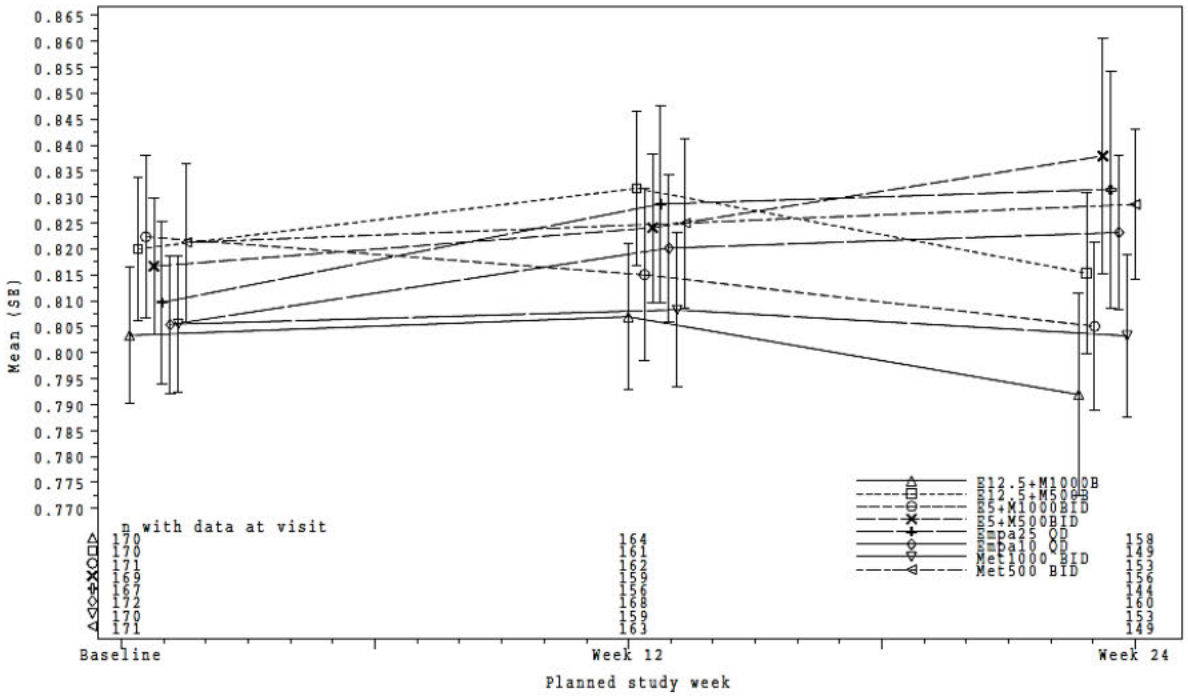
Analysis of the datasets provided by the sponsor revealed two additional patients with events in the M500 bid group (one with PT blood creatinine increased and one with PT renal injury), however, these findings do not raise any additional concerns regarding the potential of empagliflozin alone or in combination with metformin to cause renal adverse events. It is likely that the events identified during my review did not fit the protocol-specified definition for renal events.

a. Renal function based on serum creatinine

Creatinine was monitored over time and the Applicant presented descriptive statistics. Most patients had creatinine levels within normal limits at baseline, and the baseline mean values were similar between treatment groups 0.86 mg/dl for E12.5+1000 bid, 0.87 mg/dl for E12.5+M500bid, 0.87 mg/dl for E5+M1000 bid, 0.85 mg/dl for E5+M500 bid, 0.87 mg/dl for E25 qd, 0.86 mg/dl for E 10 QD, 0.93 mg/dl for M1000 bid, and 0.88 mg/dl for M500bid.

The Applicant did not report any significant changes from baseline to last value on-treatment in serum creatinine in any treatment group (Figure 5). A similar percentage of patients in all treatment groups started the study with creatinine within normal limits, and had a last value on-treatment creatinine above ULN (between 0.6 and 1.9% in various treatment groups, with no trend towards more events with empagliflozin, metformin, or the combination therapy arms) (Table 22).

Figure 5 Descriptive Statistics for Creatinine (mg/dL) Over Time by Treatment – TS



Source: Figure 15.3.2.3.1: 1 1276.1 Study report body

Table 21 Frequency of Patients (%) with Adverse Shifts in Renal Function Category (Based on Serum Creatinine) from Baseline by Treatment

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
From normal creatinine to above ULN at last value on treatment								
	2 (1.2%)	3 (1.9%)	1 (0.6%)	2 (1.3%)	2 (1.3%)	3 (1.8%)	3 (1.9%)	2 (1.3%)

Source: Modified from table 15.3.2.1:2 1276.1 Study Report Body

Two patients were reported by the Applicant with increases in creatinine values $\geq$ 2 fold from baseline and creatinine greater than ULN, one in the E12.5+M1000 bid treatment group, and one in the E5+M500 bid treatment group.

Reviewer comment: Since most of the patients enrolled in this study were relatively healthy, I am not surprised by the low frequency of shifts in creatinine, or by the low rate of renal events. Renal events with empagliflozin are already presented in the prescribing information for empagliflozin, and the low number of events from this particular study are more of a function of the population chosen for enrollment which minimizes the risk associated with the study drug. I do not think that any changes to the prescribing

information in reference to the effect on renal function are warranted based on the results of this study.

b. Renal function based on eGFR

The mean (SD) baseline eGFR values were similar across treatment groups, ranging from 90.83 (19.25) mL/min/1.73 m2 in the M500 bid group to 94.96 (20.94) mL/min/1.73 m2 in the E12.5+M5000 bid group (Table 23). Minimal increases were seen in the E12.5+M1000 bid, E5+M1000 bid, and M1000 bid groups, while small decreases were observed in the other groups (Table 23).

Table 22 Descriptive Statistics for eGFR (MDRD) (mL/min/1.73 m2) Over Time by Treatment – TS

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Number of patients, %	170 (100.0)	170 (100.0)	171 (100.0)	169 (100.0)	167 (100.0)	172 (100.0)	170 (100.0)	171 (100.0)
Baseline eGFR								
N[2] (%)	170 (100.0)	170 (100.0)	171 (100.0)	169 (100.0)	167 (100.0)	172 (100.0)	170 (100.0)	171 (100.0)
Mean (SD)	92.23 (19.24)	94.96 (20.94)	93.31 (22.01)	93.64 (22.27)	91.76 (19.81)	94.07 (21.37)	93.39 (20.10)	90.83 (19.25)
Week 24 eGFR								
N[2] (%)	158 (92.9)	149 (87.6)	153 (89.5)	156 (92.3)	144 (86.2)	160 (93.0)	153 (90.0)	149 (87.1)
Mean (SD)	95.70 (23.85)	95.07 (20.58)	95.65 (22.03)	92.42 (21.15)	90.58 (20.13)	92.23 (22.23)	95.28 (23.47)	88.56 (18.04)
Mean change[3] (SD)	3.41 (16.62)	0.28 (13.41)	2.21 (11.52)	−0.47 (13.79)	−0.75 (11.49)	−1.53 (12.28)	2.07 (12.91)	−1.66 (12.71)

[1]Original values
[2]Patients with values at this time point
[3]From baseline

Source: Table 12.2.3.2: 2 1276.1 Study report body

The Applicant reported that the analysis of mean eGFR change from baseline in subgroups of age (<50 years, 50 to <65 years, 65 to <75 years, and ≥75 years) showed a similar trend as the overall analyses, although the mean baseline eGFR values generally decreased with age, which is expected.

Adverse shifts in renal function are presented in Table 24 below. Although some differences were observed between treatment arms, they do not appear to correlate with either the dose or the treatment with metformin, empagliflozin, or both. It is notable that, although in the baseline patient characteristics there were no patients in either treatment group with moderate renal dysfunction, the Applicant appears to have used the pre-treatment eGFR rather than the screening eGFR as baseline for the shift table.

Reviewer comment: This study does not provide new information regarding renal impairment beyond what is already in the empagliflozin label.

Table 23 Frequency of Patients (%) with Adverse Shifts in Renal Function Category (Based on MDRD) from Baseline by Treatment – Treated Set

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Last eGFR value on treatment								
- From normal renal function to mild renal impairment	13 (14.1%)	13 (15.1%)	8 (9.3%)	15 (17.9%)	15 (19.7%)	17 (18.9%)	10 (12.5%)	19 (24.4%)
- From normal renal function to moderate renal impairment	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.3%)
- From normal to severe renal impairment	0 (0%)	0 (0%)	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- From mild to moderate renal impairment	2 (2.9%)	5 (7.1%)	4 (5.6%)	4 (5.5%)	2 (2.5%)	3 (4.2%)	6 (7.7%)	2 (2.5%)
- From mild to severe renal impairment	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.3%)
- From moderate to severe renal impairment	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (50%)	1 (20%)

Source: Table 12.2.3.2:3 1276.1 Study Report Body

Hepatic injury

Hepatic injury was a protocol-specified event, defined by the following alterations of liver enzyme parameters after randomization:

- Elevation of AST and/or ALT ≥3xULN combined with an elevation of total bilirubin of ≥2xULN measured in the same blood draw sample;
- Isolated elevation of AST and/or ALT ≥5xULN irrespective of any bilirubin elevation.

Only one patient in the randomized group (from the E25 qd arm) had laboratory abnormalities that matched the protocol-specified hepatic injury definition.

- Patient no (b) (6) is a 72 year old male with T2DM for less than 1 year at study start who, approximately 4.5 months after randomization, was diagnosed with moderate acute cholangitis, moderate intrahepatic duct stones, and cholelithiasis), which led to hospitalization. He underwent choledocholithotomy which led to the resolution of the event. The investigational product was not prematurely discontinued due to this event.

The Applicant also provided frequency analyses based on standardized MedDRA queries for all liver injury adverse events. Fifteen patients were identified by the Applicant with liver injury events during the treatment period. None of the identified events led to premature discontinuation of the investigational product. Only one event was an SAE (hepatic cirrhosis, patient no (b) (6) in E12.5 +M500 bid group). Per Applicant report, there were no narrow SMQ hepatic events in the E5+M500 bid group. In the other groups, the proportions of patients with hepatic injury events identified by the Applicant were as follows: 2 patients (1.2%) in each of the E12.5+M1000 bid (PTs: hepatic steatosis and hepatic enzyme increased), E25 qd (hepatic steatosis, AST increased, and GGT increased), and E10 qd group (hepatic steatosis), 3 patients (1.8%) in the E12.5+M500 bid group (hepatic steatosis, ALT increased, and hepatic cirrhosis), 1 patient (0.6%) in each of the E5+M1000 bid (ALT increased) and M1000 bid groups (hepatic steatosis), and 4 patients (2.3%) in the M500 bid group (hepatic steatosis, hepatic enzyme increased, and hyperbilirubinaemia).

My analysis using JReview and the analysis and tabulations datasets provided by the Applicant revealed similar results. There was no case that fit the Hy's Law criteria for liver injury.

Table 24 Frequency of Patients with Liver Events - TS

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total patients (%)	**171 (100.0)**	**170 (100.00)**	**171 (100.0)**	**169 (100.00)**	**167 (100.0)**	**172 (100.00)**	**169 (100.00)**	**171 (100.00)**
Patients with events (%))	**2 (1.2)**	**3 (1.8)**	**1 (0.6)**	**0 (0.0)**	**2 (1.2)**	**2 (1.2)**	**1 (0.6)**	**4 (2.3)**
Dictionary Derived Term								
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)*	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increase	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)*	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic cirrhosis	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic enzyme increased	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic steatosis	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)**	2 (1.2)	1 (0.6)	2 (1.2)
Hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)**	0 (0.0)	0 (0.0)	0 (0.0)
Hepatosplenomegaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Hyperbilirubinemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)

*, ** same patient

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

In the OL group, the Applicant did not identify any case that fit the biochemical definition for Hy's law. One patient, patient no (b) (6) was reported with ALT elevation >5X ULN approximately 3 months after initiating therapy with E12.5+M1000 bid. AST, and alkaline phosphatase were reported elevated as well. Bilirubin was normal during the event. The Applicant reports that the liver enzymes normalized approximately 2.5 months after the inception of the event, and that the investigational product was not discontinued due to this AE.

Urinary tract infections

The Applicant identified UTIs in two ways: investigator defined, and using a customized MedDRA query (BIcMQ). In each treatment group, more events were identified by the BIcMQ compared to investigator defined. The definition for investigator-defined UTI is not clear, and therefore not easily reproducible. I performed an analysis of the datasets provided by the Applicant using JReview and my results are similar to the ones the Applicant has reported using BIcMQ (however I included a few preferred terms - dysuria, nitrite urine present, urine leukocyte esterase positive - that are suggestive of UTI that were not included in the BIcMQ). As seen in Table 26 below, more patients in the combination therapy groups containing empagliflozin 12.5 mg bid had events categorized as urinary tract infections compared to either of the individual treatment groups. The patients in the E5+M1000 bid had a similar incidence of UTI events compared to the E10 qd treatment group, and fewer events when compared to the M1000 bid group. The E5+M500 bid had fewer events when compared to either of the individual components. The differences observed between the treatment groups are small and of unclear clinical significance. Notably, there were no UTI SAEs in either treatment group. Most patients only had one UTI event reported, and only 4 events led to the discontinuation of the study medication (one in the E12.5+M1000 bid group, one in the E5+M500 bid group, one in the E10 qd group, and one in the M1000 bid group).

Table 25 Frequency of Patients with Urinary Tract Infections by PT – TS

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total patients (%)	171(100.0)	170(100.0)	171(100.0)	169(100.0)	167(100.0)	172(100.0)	169(100.0)	171(100.0)
Patients with events (%)	22 (12.9)	20 (11.8)	14 (8.2)	11 (6.5)	15 (9.0)	14 (8.1)	18 (10.7)	15 (8.8)
Preferred Term								
Asymptomatic bacteriuria	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	3 (1.8)	0 (0.0)
Cystitis	1 (0.6)	2 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Dysuria	0 (0.0)	3 (1.8)	2 (1.2)	2 (1.2)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)
Genitourinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Nitrite urine present	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pyelonephritis chronic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Urinary tract infection	18 (10.5)	17 (10.0)	12 (7.0)	9 (5.3)	13 (7.8)	12 (7.0)	14 (8.3)	12 (7.0)
Urinary tract infection fungal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Urine leukocyte esterase positive	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

More females experienced UTI events in all treatment groups. In most treatment groups (with the exception of E5+M1000 bid), patients with screening HbA1c $\geq$8.5% were more likely to develop a UTI on treatment when compared to patients with screening HbA1c <8.5%. Most patients who experienced UTIs were below the age of 65, and did not have a history of recurrent UTIs.

a. Pyelonephritis:

Three patients were reported by the Applicant with pyelonephritis events, all females. Two events were reported as acute pyelonephritis (one in each E5+M1000 bid and E25 qd groups), and one with chronic pyelonephritis (M500 bid group). Brief narratives of the patients with pyelonephritis are outlined below.

- Patient no (b) (6) 46 year old female with T2DM between 1 and 5 years at study start, presented with fever, chills, and back pain approximately 2 weeks after randomization to E5+M1000 bid, and was diagnosed with acute pyelonephritis. The event was treated with ceftriaxone and ofloxacin, and was reported as resolved 1 month later.

- Patient no (b) (6) 41 year old female with T2DM for less than 1 year at study start, randomized to E25 qd, was reported with mild pyelonephritis and mild acute bronchitis four days after the last dose of trial medication. One day later, the event was reported as resolved.

- Patient no (b) (6) 47 year old female with T2DM for less than one year at study start, randomized to M500 bid. Approximately one month after randomization, the patient was reported with mild chronic bilateral pyelonephritis which was not reported as resolved at the last contact with the patient. The Applicant reported that this patient did not have any previous urinary infectious disease and that no treatment was administered.

In the OL group, there were no UTI events reported as AEs. The Applicant reported two patients with investigator-defined UTI: one with lower UTI (1.9%) and one with asymptomatic bacteriuria (1.9%). The patients did not require hospitalization or discontinuation of the study drug.

The results of the UTI analysis are consistent with the prescriber information for empagliflozin and no concerning signals are identified in the review of the current study.

Genital infections

The Applicant identified genital infections in two ways: investigator defined, and using a BIcMQ for genital infections. There were more patients with investigator-defined genital infections compared to patients that fit the BIcMQ criteria for genital infections in all the combination therapy arms, and all empagliflozin alone arms. In the metformin only groups, the number of patients identified via the two methods was the same for the M1000 bid group, and lower in the M500 bid groups for the investigator-defined events compared to the BIcMQ method. Table 27 presents the reviewer generated table which is identical to the one generated via BIcMQ method except that it identified one case of phimosis.

An imbalance in phimosis was noted in the original NDA application for empagliflozin, and this was concerning because this could be a consequence of genital infections and may require surgery for treatment. Although the Applicant did not report any case of treatment-emergent phimosis (likely because phimosis was not part of the custom BIcMQ), I identified one case using JMP clinical and JReview, in the E12.5+M500 bid group.

Table 29 Frequency of Patients N (%) with Investigator-defined Genital Infections by Treatment, Intensity, Time of Occurrence, Duration, Therapy and Action Taken – TS

	E12.5+ M1000 bid N (%)	E12.5+ M500 bid N (%)	E5+ M1000 bid N (%)	E5+ M500 bid N (%)	E25 qd N (%)	E10 qd N (%)	M1000 bid N (%)	M500 bid N (%)
Number of patients	170 (100.0)	170 (100.0)	171 (100.0)	169 (100.0)	167 (100.0)	172 (100.0)	170 (100.0)	171 (100.0)
Patients with genital infection	8 (4.7)	12 (7.1)	8 (4.7)	4 (2.4)	9 (5.4)	12 (7.0)	5 (2.9)	2 (1.2)
Intensity (worst episode)								
Mild	4 (2.4)	8 (4.7)	6 (3.5)	3 (1.8)	5 (3.0)	8 (4.7)	5 (2.9)	1 (0.6)
Moderate	4 (2.4)	4 (2.4)	2 (1.2)	1 (0.6)	3 (1.8)	4 (2.3)	0	1 (0.6)
Severe	0	0	0	0	1 (0.6)	0	0	0
Type of genital infection[1]								
Fungal balanitis or fungal vulvovaginitis	6 (3.5)	6 (3.5)	7 (4.1)	4 (2.4)	8 (4.8)	10 (5.8)	4 (2.4)	1 (0.6)
Not fungal balanitis or fungal vulvovaginitis	1 (0.6)	6 (3.5)	1 (0.6)	0	2 (1.2)	2 (1.2)	1 (0.6)	1 (0.6)
Missing	1 (0.6)	0	0	0	0	0	0	0
Time to onset of first episode, n/N at risk[2]								
Within first 3 months	6/170 (3.5)	7/170 (4.1)	7/171 (4.1)	4/169 (2.4)	7/167 (4.2)	9/172 (5.2)	2/170 (1.2)	2/171 (1.2)
After first 3 months	2/164 (1.2)	5/160 (3.1)	1/163 (0.6)	0/160	2/158 (1.3)	3/165 (1.8)	3/158 (1.9)	0/162
Therapy (worst episode)								
No therapy	1 (0.6)	3 (1.8)	1 (0.6)	0	2 (1.2)	0	1 (0.6)	0
Therapy assigned	7 (4.1)	9 (5.3)	7 (4.1)	4 (2.4)	7 (4.2)	12 (7.0)	4 (2.4)	2 (1.2)
Number of episodes per patient								
1	6 (3.5)	10 (5.9)	6 (3.5)	3 (1.8)	7 (4.2)	9 (5.2)	5 (2.9)	2 (1.2)
2	1 (0.6)	2 (1.2)	2 (1.2)	1 (0.6)	1 (0.6)	2 (1.2)	0	0
3 or 4	1 (0.6)	0	0	0	0	1 (0.6)	0	0
5 or more	0	0	0	0	1 (0.6)	0	0	0
Leading to discontinuation[3]	1 (0.6)	1 (0.6)	0	1 (0.6)	1 (0.6)	0	0	0
Resolved genital infection	6 (3.5)	8 (4.7)	8 (4.7)	4 (2.4)	6 (3.6)	11 (6.4)	4 (2.4)	2 (1.2)

[1]Patients can be counted in more than 1 category.
[2]N at risk is the number of patients with at least 1 day in the period of interest when AEs would be considered on-treatment.
[3]Premature discontinuation of study medication

Source: Table 12.2.3.5:2 1276.1 Study report body

Table 26 Frequency of Patients with Genital Infections by PT – TS

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total patients (%)	171 (100.0)	170 (100.0)	171 (100.0)	169 (100.0)	167 (100.0)	172 (100.0)	169 (100.0)	171 (100.0)
Patients with events (%)	5 (2.9)	9 (5.3)	6 (3.5)	4 (2.4)	9 (5.4)	13 (7.6)	7 (4.1)	5 (2.9)
Preferred Term								
Bacterial vaginosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Balanitis candida	0 (0.0)	0 (0.0)	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
Balanoposthitis	0 (0.0)	3 (1.8)	0 (0.0)	1 (0.6)	1 (0.6)	5 (2.9)	0 (0.0)	0 (0.0)
Candida infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cervicitis	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Fungal cystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Genital burning sensation	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Genital candidiasis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Genital infection	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Genital infection fungal	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Genital infection male	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Genital infection viral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Genitourinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.2)	1 (0.6)
Perineal abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Phimosis	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vaginal infection	3 (1.8)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)
Vulvitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)
Vulvovaginal candidiasis	1 (0.6)	1 (0.6)	2 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	2 (1.2)
Vulvovaginal mycotic infection	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	3 (1.8)	3 (1.7)	1 (0.6)	0 (0.0)
Vulvovaginitis	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

Most patients only had one episode of genital infection. Four patients were reported to have discontinued the study treatment due to genital infections, one in each E12.5+M1000 bid, E12.5+M500 bid, E5+M500 bid, and E25 qd treatment groups. No male patients were reported with genital infection in the E12.5+M1000 bid, M1000 bid, and M500 bid groups. In all other treatment groups, the proportion of males with genital infections almost equaled the proportion of women. Patients who were less than 65 years of age were more likely to experience genital infections in most treatment groups. No dose dependence was observed. This is consistent with the prescribing information for empagliflozin.

Table 27 Frequency of Patients with Genital Infections by Sex, Age, and Baseline HbA1c

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total patients	171	170	171	169	167	172	169 (100.0)	171 (100.0)
(%)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)		
Patients with events (%)	5 (2.9)	9 (5.3)	6 (3.5)	4 (2.4)	8 (4.8)	11 (6.4)	5 (3.0)	4 (2.3)
Sex								
F	5 (2.9)	5 (2.9)	3 (1.8)	2 (1.2)	5 (3.0)	5 (2.9)	5 (3.0)	4 (2.3)
M	0 (0.0)	4 (2.4)	3 (1.8)	2 (1.2)	3 (1.8)	6 (3.5)	0 (0.0)	0 (0.0)
Age								
<65	5 (2.9)	8 (4.7)	3 (1.8)	2 (1.2)	6 (3.6)	10 (5.8)	5 (3.0)	4 (2.3)
>=65	0 (0.0)	1 (0.6)	3 (1.8)	2 (1.2)	2 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)
HbA1c								
<8.5	4 (2.3)	4 (2.4)	3 (1.8)	3 (1.8)	5 (3.0)	7 (4.1)	2 (1.2)	1 (0.6)
>=8.5	1 (0.6)	5 (2.9)	3 (1.8)	1 (0.6)	3 (1.8)	4 (2.3)	3 (1.8)	3 (1.8)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

In the OL group, 2 patients (3.8%) were reported with investigator-defined genital infections (single episodes). Both events belonged to the category fungal balanitis or fungal vulvovaginitis. Neither event was severe or lead to study drug discontinuation.

Volume depletion

The Applicant presented AEs possibly related to volume depletion identified using a BIcMQ. The results of this analysis are presented in Table 29 below. The Applicant also reported that the distribution of volume depletion events was similar across age subgroups. Of the 9 patients identified by the Applicant, 2 had normal renal function at baseline, and 7 had mild renal impairment.

Table 28 Patients with Volume Depletion Events Reported by the Applicant - TS

User-defined AE category/ Preferred term	E12.5+M1000B N (%)	E12.5+M500B N (%)	E5+M1000BID N (%)	E5+M500BID N (%)	Empa25 QD N (%)	Empa10 QD N (%)	Met1000 BID N (%)
Number of patients	170 (100.0)	170 (100.0)	171 (100.0)	169 (100.0)	167 (100.0)	172 (100.0)	170 (100.0)
Total with volume depletion	3 (1.8)	0 (0.0)	1 (0.6)	2 (1.2)	1 (0.6)	0 (0.0)	2 (1.2)
Volume depletion	3 (1.8)	0 (0.0)	1 (0.6)	2 (1.2)	1 (0.6)	0 (0.0)	2 (1.2)
Dehydration	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Hypotension	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)
Orthostatic hypotension	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)

Percentages are calculated using total number of patients per treatment as the denominator.
Containing data from study 1276_0001
MedDRA version used for reporting: 17.1

Source Table 15.3.1.9: 1 1276.1 Study report body

However, the Applicant BIcMQ did not include preferred terms that can suggest volume depletion such as dizziness, vertigo, loss of consciousness. I analyzed the datasets using JReview and including the above mentioned preferred terms (in addition to those from the BIcMQ). The results are presented in Table 30 below. No clear trends can be observed between the different treatment groups, and none of the volume depletion events was an SAE.

Table 29 Patients with Volume Depletion Events – Reviewer Generated

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total patients (%)	171(100.0)	170(100.0)	171(100.0)	169(100.0)	167(100.0)	172(100.0)	169(100.0)	171(100.0)
Patients with events (%)	9(5.3)	9(5.3)	7(4.1)	7(4.1)	4(2.4)	5(2.9)	5(3.0)	9(5.3)
Preferred Term								
Dehydration	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
Dizziness	6(3.5)	9(5.3)	4(2.3)	5(3.0)	3(1.8)	4(2.3)	4(2.4)	7(4.1)
Dizziness postural	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)
Hypotension	1(0.6)	0(0.0)	0(0.0)	1(0.6)	1(0.6)	0(0.0)	1(0.6)	0(0.0)
Loss of consciousness	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Orthostatic hypotension	1(0.6)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Syncope	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	1(0.6)	0(0.0)
Vertigo	0(0.0)	0(0.0)	1(0.6)	1(0.6)	0(0.0)	1(0.6)	0(0.0)	1(0.6)
Vertigo positional	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

In the OL group, 1 patient (1.9%) was reported with hypotension.

Diabetic ketoacidosis

There were no reported cases of diabetic ketoacidosis or acidosis. One case of ketonuria was reported in the E5+M500 BID treatment group.

Reviewer comment: There is no safety signal regarding DKA from the currently reviewed study. Based on post-marketing reports, however, this is an important concern and led to a safety labeling change for all SGLT2 inhibitor drugs that are currently FDA approved.

Fractures

The Applicant reported bone fractures in two ways: investigator-defined (unclear how defined), and based on a BIcMQ. Per Applicant report, 5 patients were reported with investigator-defined bone fractures (1 patient each in the E12.5+M1000 bid, E12.5+M500 bid, and E10 qd groups, and 2 patients in the E5+M1000 bid group, all listed as traumatic), while 8 patients were reported with AE of bone fracture based on the BIcMQ. Using the datasets provided by the Applicant and JReview, I generated Table 31 below, which is identical to the one provided by the Applicant using the BIcMQ. Only the two subjects with PT rib fracture are listed as falls, (one fell off a ladder, and one reported as accidental fall), while the other fractures (except for the tooth fracture events) are listed as traumatic. In conclusion, with the limited data available, it is difficult to understand the causality of the reported fracture events.

Focusing on falls, JReview analysis selecting patients who were listed with the MedDRA preferred term of fall reveals only three patients (one in each E10 qd, E25 qd, and M500 bid treatment groups), and these are not the patients that were reported with fractures following a fall. Therefore, I am concerned that not all the fall events were correctly coded under falls. There are no narratives submitted specifically for fall events, and the only fracture narrative available is for an SAE - patient no (b) (6) who suffered a rib fracture falling from a ladder.

There were no fracture events reported in the open label group.

Notably, there were no AEs of fractures in either of the metformin only arms, while most arms containing empagliflozin did report 1-2 subjects with fractures (with the exception of the E5 + M500 bid arm). The significance of this numerical imbalance is not clear as the event numbers are very small and making the results inconclusive. However, fractures remain a concern with the entire class of SGLT2 inhibitors.

Table 30 Patients with Fracture Events

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total patients (%)	171(100.0)	170(100.0)	171(100.0)	169(100.0)	167(100.0)	172(100.0)	169(100.0)	171(100.0)
Patients with event (%)	2(1.2)	2(1.2)	2(1.2)	0(0.0)	1(0.6)	1(0.6)	0(0.0)	0(0.0)
Preferred Term								
Facial bones fracture	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
Foot fracture	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Hand fracture	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Rib fracture	0(0.0)	0(0.0)	2(1.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Tooth fracture	0(0.0)	1(0.6)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Wrist fracture	1(0.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

Malignancy events

The Applicant stated that malignancy events were monitored until last contact. Only two patients are reported with malignancies in the treated set. One patient in the E12.5+M1000 bid group was reported with metastases to liver (post-treatment) and 1 patient in the E12.5+M500 bid group was reported with chronic lymphatic leukemia (on-treatment). There were no bladder cancer events in this study.

No malignancies were reported in the open label group.

Malignancy events were explored by using JReview and the datasets provided by the Applicant. The reviewer generated results match the events reported by the Applicant.

Due to exceedingly small number of events, it is not possible to draw any conclusion at this time. There is no information from this study that increases the level of concern regarding increase in malignancy with empagliflozin, or metformin.

Other significant AEs

The Applicant submitted an analysis of other significant AEs included those non-serious AEs that led to premature discontinuation of trial medication or that were marked as other significant by the investigator or by the BI clinical monitor. AEs leading to discontinuation were discussed in Section 7.3.3.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events experienced by ≥2% of patients in either treatment group are presented in Table 32 below. The cutoff criteria of ≥2% is arbitrary, but is commonly used across Applicants and drug categories to define common adverse events. There were 82 (48%), 73 (42.9%), 54 (31.6%), and 74 (43.8%) patients with common AEs in each E12.5+M1000 bid, E12.5+M500 bid, E5+M1000 bid, and E5+M500 bid treatment groups respectively. In the remaining four treatment groups, there were 71 (41.3%), 63 (37.7%), 74 (43.8%), and 67 (39.2%) patients with common AEs in E25 qd, E10 qd, M1000 bid, and M500 bid groups. At the preferred term (PT) level, patients were most frequently reported with urinary tract infection, upper respiratory tract infection, dyslipidemia, dizziness, and diarrhea (>5% at PT level in any treatment group). The overall distribution of common AEs was relatively balanced between treatment groups, however some differences were noted at PT level as follows: more patients in the groups either on empa alone or combination therapy experienced constipation, while more patients in the M1000 bid group experienced diarrhea. There was also more nausea observed in the combination therapy groups compared to single drug groups, and more UTI events in both combination therapy groups containing empagliflozin12.5 bid when compared to the other treatment groups. There were more hyperglycemia events reported in the single drug groups compared to combination therapy groups, and more hypoglycemia in the combination treatment groups containing empagliflozin 12.5 bid.

Table 31 Adverse Events Occurring in >2% of Patients in Either Treatment Group

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total patients (%)	171(100)	170(100)	171(100)	169(100)	172(100)	167(100)	169(100)	171(100)
Patients with events (%)	82(48.0)	73(42.9)	54(31.6)	74(43.8)	71(41.3)	63(37.7)	74(43.8)	67(39.2)
System Organ Class/Preferred Term								
Gastrointestinal disorders								
Abdominal distension	1(0.6)	2(1.2)	4(2.3)	2(1.2)	1(0.6)	1(0.6)	1(0.6)	1(0.6)
Abdominal pain upper	2(1.2)	4(2.4)	2(1.2)	2(1.2)	1(0.6)	2(1.2)	1(0.6)	0(0.0)

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Constipation	6(3.5)	0(0.0)	4(2.3)	2(1.2)	2(1.2)	3(1.8)	1(0.6)	1(0.6)
Diarrhea	12(7.0)	6(3.5)	5(2.9)	9(5.3)	2(1.2)	6(3.6)	24(14.2)	6(3.5)
Nausea	6(3.5)	4(2.4)	5(2.9)	5(3.0)	1(0.6)	1(0.6)	3(1.8)	1(0.6)
General disorders and administration site conditions								
Pain	0(0.0)	4(2.4)	1(0.6)	1(0.6)	1(0.6)	1(0.6)	1(0.6)	0(0.0)
Infections and infestations								
Gastroenteritis	2(1.2)	2(1.2)	2(1.2)	1(0.6)	5(2.9)	3(1.8)	2(1.2)	1(0.6)
Influenza	2(1.2)	2(1.2)	2(1.2)	4(2.4)	2(1.2)	3(1.8)	5(3.0)	4(2.3)
Nasopharyngitis	6(3.5)	5(2.9)	3(1.8)	6(3.6)	5(2.9)	3(1.8)	3(1.8)	3(1.8)
Upper respiratory tract infection	4(2.3)	5(2.9)	8(4.7)	4(2.4)	5(2.9)	7(4.2)	4(2.4)	10(5.8)
Urinary tract infection	18(10.5)	17(10.0)	12(7.0)	9(5.3)	12(7.0)	13(7.8)	14(8.3)	12(7.0)
Urinary trac tinfection fungal	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)	0(0.0)
Investigations								
Blood creatine phosphokinase increased	1(0.6)	4(2.4)	4(2.3)	2(1.2)	1(0.6)	1(0.6)	1(0.6)	0(0.0)
C-reactive protein increased	3(1.8)	0(0.0)	1(0.6)	2(1.2)	2(1.2)	0(0.0)	4(2.4)	1(0.6)
Metabolism and nutrition disorders								
Dyslipidemia	8(4.7)	6(3.5)	8(4.7)	15(8.9)	15(8.7)	11(6.6)	8(4.7)	7(4.1)
Hyperglycemia	0(0.0)	1(0.6)	1(0.6)	1(0.6)	3(1.7)	4(2.4)	3(1.8)	7(4.1)
Hypertriglyceridemia	2(1.2)	3(1.8)	0(0.0)	5(3.0)	3(1.7)	1(0.6)	2(1.2)	2(1.2)
Hyperuricemia	0(0.0)	3(1.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	7(4.1)	1(0.6)
Hypoglycemia	4(2.3)	4(2.4)	1(0.6)	0(0.0)	2(1.2)	1(0.6)	2(1.2)	0(0.0)
Musculoskeletal and connective tissue disorders								
Arthralgia	3(1.8)	6(3.5)	0(0.0)	1(0.6)	3(1.7)	5(3.0)	4(2.4)	1(0.6)
Back pain	8(4.7)	1(0.6)	4(2.3)	4(2.4)	5(2.9)	0(0.0)	5(3.0)	4(2.3)
Musculoskeletal pain	1(0.6)	3(1.8)	0(0.0)	3(1.8)	4(2.3)	4(2.4)	1(0.6)	2(1.2)
Pain in extremity	4(2.3)	1(0.6)	2(1.2)	0(0.0)	4(2.3)	8(4.8)	4(2.4)	5(2.9)
Nervous system disorders								
Dizziness	6(3.5)	9(5.3)	4(2.3)	5(3.0)	4(2.3)	3(1.8)	4(2.4)	7(4.1)
Headache	8(4.7)	8(4.7)	6(3.5)	7(4.1)	5(2.9)	6(3.6)	4(2.4)	5(2.9)
Renal and urinary disorders								
Pollakiuria	0(0.0)	1(0.6)	0(0.0)	4(2.4)	0(0.0)	2(1.2)	1(0.6)	0(0.0)
Reproductive system and breast disorders								
Balanoposthitis	0(0.0)	3(1.8)	0(0.0)	1(0.6)	5(2.9)	1(0.6)	0(0.0)	0(0.0)
Skin and subcutaneous tissue disorders								
Pruritus	2(1.2)	0(0.0)	0(0.0)	0(0.0)	1(0.6)	4(2.4)	1(0.6)	0(0.0)
Rash	4(2.3)	1(0.6)	1(0.6)	1(0.6)	0(0.0)	1(0.6)	1(0.6)	0(0.0)
Vascular disorders								
Hypertension	5(2.9)	5(2.9)	1(0.6)	6(3.6)	2(1.2)	4(2.4)	3(1.8)	8(4.7)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

The most common AEs in the OL group (>25% of patients reported with these AEs at SOC level) belonged to the SOCs 'gastrointestinal disorders' (17 patients, 32.1%) and 'infections and infestations' (14 patients, 26.4%). The most common PT was diarrhea (4 patients, 7.5%).

7.4.2 Laboratory Findings

Standard laboratory parameters were measured at regular intervals during the study, all samples were collected after an overnight fast and before the trial medication and the samples were analyzed by a central laboratory. Safety laboratory tests at follow-up visits were only performed in association with clinic visits and not with telephone visits. For the OL group, only limited clinical laboratory data were collected and analyzed.

The Applicant submitted descriptive statistics for electrolytes, hematology parameters, uric acid, and lipid parameters.

Laboratory evaluations of hepatic and renal functions are described above.

Electrolytes

For evaluation of electrolytes, changes in serum sodium, potassium, calcium, magnesium, chloride, phosphate, and bicarbonate were examined. No significant change in median values from baseline was reported for any of these laboratory tests.

Table 32 Incidence of Selected Categorical Shifts - Electrolytes

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
From WRR at baseline to above ULRR at last observation on treatment								
Sodium	2(1.2)	4(2.6)	0(0)	1(0.6)	2(1.3)	3(1.8)	0(0)	2(1.3)
Potassium	1(0.6)	2(1.3)	0(0)	0(0)	1(0.7)	2(1.2)	0(0)	5(3.1)
Calcium	6(3.8)	4(2.6)	7(4.4)	6(3.9)	6(3.9)	2(1.2)	6(3.9)	1(0.6)
Magnesium	0(0)	0(0)	0(0)	2(1.3)	0(0)	0(0)	0(0)	0(0)
Chloride	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Phosphate	5(3.0)	3(1.9)	3(1.9)	1(0.6)	2(1.3)	4(2.4)	2(1.3)	2(1.2)
Bicarbonate	2(1.6)	1(1.0)	2(1.9)	0(0)	0(0)	1(0.8)	2(1.9)	1(0.9)
From WRR at baseline to below LLRR at last observation on treatment								
Sodium	0(0)	1(0.6)	0(0)	0(0)	0(0)	0(0)	0(0)	1(0.6)
Potassium	0(0)	0(0)	1(0.6)	2(1.3)	2(1.3)	1(0.6)	3(1.9)	0(0)
Calcium	3(1.9)	3(1.9)	2(1.3)	1(0.6)	2(1.3)	1(0.6)	1(0.7)	3(1.9)
Magnesium	0(0)	3(1.9)	3(2.0)	1(0.7)	1(0.6)	0(0)	6(3.9)	3(1.9)

Chloride	1(0.6)	1(0.6)	0(0)	1(0.6)	2(1.3)	2(1.2)	3(1.9)	2(1.2)
Phosphate	0(0)	0(0)	0(0)	0(0)	1(0.6)	0(0)	0(0)	1(0.6)
Bicarbonate	41(33.1)	31(29.5)	26(25)	28(26.4)	24(22.9)	28(23.5)	25(23.4)	29(25.2)

WRR = within reference range; ULRR = upper limit of reference range; LLRR = lower limit of reference range
Source: Modified from Table 15.3.2.1:2 1276.1 Study Report Body

The Applicant identified patients with possible clinically significant abnormalities by treatment, defined as follows : for sodium – below 130 mEq/L and above 160 mEq/L, potassium – below 3 mEq/L and above 6 mEq/L, calcium – below 7.2 mg/dl and above 12 mg/dl, for chloride – below 80 mEq/L and above 120 mEq/L, phosphate – below 2.2 mg/dl and above 5.3 mg/dl, and bicarbonate – below 18 mEq/L and above 32 mEq/L There were none, or very few clinically significant shifts for sodium, potassium, calcium, magnesium, and chloride. There were more shifts in bicarbonate from WRR at baseline to below LLRR at last value on treatment in the E12.5+M bid treatment groups when compared to the other groups, however the differences are small, and the E25 qd group did not appear to be different when compared to the metformin monotherapy groups. There were more patients with potentially clinically significant increases in phosphate in the treatment groups containing empagliflozin compared to metformin only groups: 10 (1.5%) of patients in the empa+met groups, 5 (1.5%) in the empagliflozin groups, and 2 (0.6%) in the metformin only groups.

For bicarbonate, the applicant identified 15(9.3%) patients in the E12.5+ M1000 bid group, 12(7.7%), 12 (7.5%), 13 (8.3%), 8 (5.3%), and 6 (3.7%) in the E12.5+ M500 bid, E5+ M1000 bid, E5+ M500 bid, E25 qd, and E10 qd groups respectively with clinically significant abnormalities. In the metformin groups, there were 15 (9.6%) patients in the M1000 bid group, and 4 (2.5) patients in the M500 bid group.

Hematology

In the original NDA review for empagliflozin, a small increase in hematocrit was observed in the empagliflozin groups from baseline to the last value on treatment. While this increase was not observed in the placebo or comparator groups, it did not lead to an increase in thromboembolic or vascular events. Consistent with this previous finding, an increase in hematocrit was observed in the study 1276.1 in all treatment groups containing empagliflozin (combination and single drug therapy), while minimal decreases in hematocrit were observed in the metformin only groups. The percent change compared to baseline in hematocrit is presented in Table 34below for all treatment groups. Notably, all empagliflozin containing arms resulted in a similar percent increase in hematocrit compared to baseline (3.3 to 3.9%), regardless of the daily empagliflozin dose.

Table 33 Descriptive Statistics for Hematocrit – TS

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Number of patients [1]	165/170	165/170	161/171	160/169	158/167	168/172	158/170	162/171
Mean (SD) [%] [2]								
Baseline	44.8 (4.6)	45.3 (5.1)	45.7 (4.3)	45.0 (5.2)	45.6 (5.4)	45.4 (5.0)	45.0 (5.3)	45.6 (4.8)
Last value on-treatment	46.6 (4.9)	47.7 (5.0)	47.9 (5.1)	47.8 (5.2)	48.6 (5.6)	48.6 (5.3)	43.6 (5.5)	45.2 (4.8)
Difference from baseline	1.8 (3.3)	2.4 (3.9)	2.2 (3.5)	2.8 (3.8)	3.0 (3.9)	3.1 (3.8)	−1.5 (3.3)	−0.4 (3.1)

[1] Number of patients with value / total number of treated patients
[2] Normalised values
Source: table 12.3:1 study report body

A smaller proportion of patients with normal hematocrit values at baseline showed transitions to >ULN values at the end-of-treatment in the E12.5+M1000 bid group (4.4%) and in the E12.5+M500 bid group (12.4%) than in the E 25 qd group (15.7%). In the E5+M bid groups, the proportion of patients with such shifts was higher in the E5+M1000 bid group (12.1%) than in the E10 qd group (9.7%) and comparable between the E5+M500 bid group (9.3%) and the E10 qd group. Shifts to >ULN were rare in the metformin groups (1 patient in the M1000 bid group and 2 patients in the M500 bid group).

Table 34 Incidence of Categorical Shifts–Treated set – Hematocrit

Baseline value	**Last value on treatment**		
	Below LLRR	**WRR**	**Above ULRR**
E12.5+M1000 bid			
Below LLRR	1(25.0)	3(75.0)	0
WRR	1(0.6)	150(94.9)	7(4.4)
Above ULRR	0	0	3(100.0)
E12.5+M500 bid			
Below LLRR	3(42.9)	4(57.1)	0
WRR	0	127(87.6)	18(12.4)
Above ULRR	0	4(50.0)	4(50.0)
E5+M1000 bid			
Below LLRR	0	1(100.0)	0
WRR	0	138(87.9)	19(12.1)
Above ULRR	0	1(33.3)	2(66.7)
E5+M500 bid			
Below LLRR	3(60.0)	2(40.0)	0
WRR	0	136(90.7)	14(9.3)
Above ULRR	0	0	5(100.0)
E25 qd			
Below LLRR	0	5(100.0)	0

WRR	1(0.7)	117(83.6)	22(15.7)
Above ULRR	0	3(23.1)	10(76.9)
E10 qd			
Below LLRR	1(20.0)	4(80.0)	0
WRR	1(0.6)	138(89.6)	15(9.7)
Above ULRR	0	2(22.2)	7(77.8)
M1000 bid			
Below LLRR	3(75.0)	1(25.0)	0
WRR	8(5.4)	138(93.9)	1(0.7)
Above ULRR	0	4(57.1)	3(42.9)
M500 bid			
Below LLRR	0	1(100.0)	0
WRR	2(1.3)	150(97.4)	2(1.3)
Above ULRR	0	4(57.1)	3(42.9)

Source: Modified from Table 15.3.2.1:2 1276.1 Study Report Body

Possibly clinically significant abnormalities (PCSAs) in the high range were overall rare: 1 patient each (0.6%) for E12.5+M500 bid, E5+M500 bid, and E10 qd; 2 patients each for E5+M1000 bid (1.2%) and M1000 bid (1.3%); 5 patients (3.2%) in the E25 qd group; no patient in the E12.5+M1000 bid and M500 bid groups.

Despite the increase in hematocrit in the treatment groups containing empagliflozin, only one patient was reported with a thromboembolic event, in the E12.5+M1000 bid group. The patient is patient no (b) (6) a 51 year old male who was reported with retinal vein occlusion on day 134 of treatment, which did not lead to premature discontinuation of treatment. It is reassuring that, despite the hematocrit increase, there does not seem to be a correlation with thrombotic events.

Uric acid

Serum uric acid values decreased at week 24 from baseline in all treatment groups containing empagliflozin, which is consistent with the trend observed in the original NDA review. This may indicate uricosuria due to treatment with empagliflozin, signaling a potential for causing renal insufficiency/impairment. In contrast, uric acid values increased from baseline to week 24 in the metformin groups.

There were only two patients with clinically significant abnormalities in uric acid, both in the M1000 bid treatment group. The incidence of categorical shifts for uric acid is presented below in Table 36

Table 35 Incidence of Categorical Shifts – Uric Acid

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
From WRR at baseline to above ULRR at last observation on treatment	2(1.4)	2(1.4)	1(0.7)	2(1.4)	1(0.7)	3(1.9)	16(11.2)	12(17.9)
From WRR at baseline to below LLRR at last observation on treatment	5(3.4)	3(2.1)	3(2.1)	1(0.7)	3(2.0)	5(3.1)	2(1.4)	0

Source: Modified from table 15.3.2.1:2 1276.1 Study report body

Serum lipids

Dyslipidemia is often seen in conjunction with diabetes mellitus, and is a risk factor for cardiovascular disease. In the original empagliflozin NDA review, several dose-dependent changes of unknown clinical significance were noted in lipid parameters: dose-dependent increase from baseline in total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and non-HDL cholesterol with empagliflozin treatment compared to placebo at 24 and 52 weeks.

Compared to the findings during the initial NDA review, the change from baseline in lipid parameters at 24 weeks in study 1276.1 are somewhat different. Small increases from baseline to Week 24 were noted for HDL-cholesterol in all treatment groups. For LDL-cholesterol, increases were noted in the E12.5+M500 bid and empagliflozin monotherapy groups; decreases from baseline to Week 24 in LDL-cholesterol values were noted in the other groups. See Table 37 below for details.

The proportions of patients with shifts in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides from normal values at baseline to >ULN at last observation on treatment are presented in Table 38 below. It appears that there were more patients who had an increase in HDL-cholesterol to >ULN in all the treatment groups containing empagliflozin when compared to the metformin only groups. It is very difficult to identify any drug or dose-related trends regarding the other lipid parameters presented in the Table 38 below.

Table 36 Change in Lipids from Baseline to Week 24, MMRM (OC-IR) – TS

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Total cholesterol								
Number of patients[1]	158/170	149/170	154/171	155/169	141/167	157/172	150/170	151/171
Baseline, mean (SE) [mg/dL]	198.33 (3.34)	187.72 (2.93)	193.83 (3.52)	192.92 (3.99)	188.56 (3.18)	195.29 (3.30)	197.79 (4.68)	195.77 (3.08)
Mean (SE) adjusted change at Week 24 [mg/dL][2]	−0.90 (2.62)	3.03 (2.69)	1.46 (2.65)	6.59 (2.65)	11.65 (2.75)	3.33 (2.62)	−4.71 (2.68)	2.73 (2.66)
HDL-cholesterol								
Number of patients[1]	158/170	148/170	154/171	155/169	141/167	158/172	150/170	151/171
Baseline, mean (SE) [mg/dL]	45.57 (0.95)	45.13 (0.98)	44.97 (0.85)	46.17 (1.04)	46.54 (0.87)	45.18 (0.95)	46.86 (1.05)	45.76 (0.85)
Mean (SE) adjusted change at Week 24 [mg/dL][3]	4.88 (0.63)	5.47 (0.64)	4.18 (0.63)	4.76 (0.63)	3.80 (0.66)	4.77 (0.63)	1.86 (0.64)	2.46 (0.64)
LDL-cholesterol								
Number of patients[1]	157/170	148/170	154/171	153/169	141/167	157/172	148/170	151/171
Baseline, mean (SE) [mg/dL]	118.25 (2.93)	108.33 (2.55)	113.92 (2.73)	111.82 (3.38)	108.84 (2.61)	113.24 (2.79)	116.05 (3.94)	115.39 (2.66)
Mean (SE) adjusted change at Week 24 [mg/dL][4]	−5.04 (2.18)	1.10 (2.24)	−2.61 (2.20)	−0.83 (2.21)	7.71 (2.28)	1.86 (2.18)	−10.84 (2.24)	−2.27 (2.21)
HDL-cholesterol/LDL-cholesterol ratio								
Number of patients[1]	157/170	148/170	154/171	153/169	141/167	157/172	148/170	151/171
Baseline, mean (SE)	2.73 (0.08)	2.58 (0.09)	2.65 (0.08)	2.55 (0.08)	2.44 (0.07)	2.65 (0.08)	2.60 (0.09)	2.65 (0.07)
Mean (SE) adjusted change at Week 24[5]	−0.37 (0.05)	−0.22 (0.05)	−0.26 (0.05)	−0.26 (0.05)	0.01 (0.06)	−0.18 (0.05)	−0.35 (0.06)	−0.17 (0.05)
Non-HDL-cholesterol								
Number of patients[1]	158/170	148/170	154/171	155/169	141/167	157/172	150/170	151/171
Baseline, mean (SE) [mg/dL]	152.76 (3.23)	142.59 (2.89)	148.86 (3.52)	146.75 (3.90)	142.04 (3.13)	150.11 (3.30)	150.92 (4.66)	150.01 (3.05)
Mean (SE) adjusted change at Week 24 [mg/dL][6]	−5.84 (2.61)	−2.01 (2.68)	−2.56 (2.63)	1.78 (2.64)	7.69 (2.73)	−1.41 (2.61)	−6.78 (2.67)	0.24 (2.65)
Triglycerides								
Number of patients[1]	158/170	149/170	154/171	155/169	141/167	157/172	150/170	151/171
Baseline, mean (SE) [mg/dL]	176.56 (7.85)	178.39 (9.07)	185.14 (13.86)	187.07 (11.54)	167.18 (8.62)	194.42 (15.25)	177.73 (10.26)	176.74 (7.51)
Mean (SE) adjusted change at Week 24 [mg/dL][7]	−2.48 (8.99)	−20.47 (9.22)	−3.29 (9.09)	15.08 (9.11)	2.91 (9.42)	−15.80 (9.01)	21.29 (9.21)	10.71 (9.14)

[1]Number of patients with value at Week 24/ total number of treated patients
[2]The model included baseline total cholesterol (p<0.0001) and baseline HbA_{1c} (p=0.0525) as linear covariates, and baseline eGFR (p=0.4973), geographical region (p=0.0043), treatment (p<0.0001), visit (p=0.0004), and visit-by-treatment interaction (p=0.8645) as fixed effects. The covariance matrix was unstructured.
[3]The model included baseline HDL-cholesterol (p<0.0001) and baseline HbA_{1c} (p=0.0135) as linear covariates, and baseline eGFR (p=0.0058), geographical region (p=0.2354), treatment (p=0.0014), visit (p<0.0001), and visit-by-treatment interaction (p=0.1945) as fixed effects. The covariance matrix was unstructured.
[4]The model included baseline LDL cholesterol (p<0.0001) and baseline HbA_{1c} (p=0.0345) as linear covariates and baseline eGFR (p=0.4976), geographical region (p=0.0094), treatment (p<0.0001), visit (p=0.0465), and visit-by-treatment interaction (p=0.7507) as fixed effects. The covariance matrix was unstructured.
[5]The model included baseline LDL/HDL-cholesterol ratio (p<0.0001) and baseline HbA_{1c} (p=0.0062) as linear covariates, and baseline eGFR (p=0.1850), geographical region (p=0.2611), treatment (p<0.0001), visit (p=0.0138), and visit-by-treatment interaction (p=0.3783) as fixed effects. The covariance matrix was unstructured.
[6]The model included baseline non-HDL-cholesterol (p<0.0001) and baseline HbA_{1c} (p=0.0171) as linear covariates, and baseline eGFR (p=0.7236), geographical region (p=0.0051), treatment (p=0.0002), visit (p=0.1143), and visit-by-treatment interaction (p=0.7973) as fixed effects. The covariance matrix was unstructured.
[7]The model included baseline triglycerides (p<0.0001), baseline HbA_{1c} (p=0.3024) as linear covariates, and baseline eGFR (p=0.5967), geographical region (p=0.0205), treatment (p=0.0617), visit (p=0.1502), and visit-by-treatment interaction (p=0.2238) as fixed effects. The covariance matrix was unstructured.

Source: Table 12.3:3 1276.1 Study Report Body

Table 37 Selected Categorical Shifts - Cholesterol

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
From WRR at baseline to above ULRR at last observation on treatment								
Total cholesterol	12 (12.5)	24 (23.3)	23 (25.3)	14 (16.9)	21 (22.1)	17 (18.5)	14 (16.3)	26 (28.3)
HDL-cholesterol	6 (5.9)	2 (2.0)	2 (1.9)	3 (2.9)	2 (1.8)	2 (1.9)	0	1 (0.9)
LDL-cholesterol	9 (8.0)	21 (16.9)	20 (17.1)	18 (15.7)	23 (20.4)	14 (12.2)	10 (9.2)	19 (16.1)
Triglycerides	13 (9.1)	6 (4.4)	12 (8.8)	15 (11.1)	13 (9.6)	5 (3.6)	15 (11.2)	15 (10.9)

Source: Table 12.3:4 1276.1 Study report body

The proportion of patients with PCSA high values of total cholesterol was 6.8% in the E12.5+M1000 bid group, 8.4% in the E12.5+M500 bid group, 7.4% in the E5+M1000 bid group, 10.5% in the E5+M500 bid group, 11.8% in the M500 bid group. The proportion in all empagliflozin groups was 11.9%, 8.3% in all empagliflozin+metformin, and in the metformin only groups was 8.8%. The frequencies of patients with PCSA high values of triglycerides varied from 8 patients (5.5%) for M1000 bid to 18 patients (11.8%) for E25 qd and M500 bid. The proportion in all empagliflozin groups was 9.5%, all empagliflozin+metformin was 6.9%, metformin only groups was 10.5%. Possibly clinically significant abnormal values were not defined for other lipid parameters.

In the OL group, the Applicant reported that the mean (SD) lipid changes analyzed with LOCF-IR were: −23.30 (30.56) mg/dL for total cholesterol, 4.83 (7.42) mg/dL for HDL-cholesterol , −20.34 (27.28) mg/dL for LDL-cholesterol, −0.76 (0.87) for the LDL-cholesterol/HDL-cholesterol ratio , −28.14 (31.04) mg/dL for non-HDL-cholesterol, and −46.43 (132.87) mg/dL for triglycerides.

Overall the changes are small and of unclear clinical relevance. For many parameters, there are inconsistencies in the trends observed with treatment groups that are similar, and this cannot be explained mechanistically. It is therefore likely to be due to chance. While the study enrolled a relatively large number of patients overall, the sample size per treatment groups is small and it probably contributes to inconsistent results.

7.4.3 Vital Signs

Vitals signs measured as part of this study included heart rate (HR), BP, and weight. Changes in BP and weight were discussed as secondary efficacy endpoints in sections 6.2.6.1 and 6.2.5.2, respectively.

The mean pulse rate was similar between the treatment groups at baseline. There were no significant changes in pulse rates over time in either treatment group.

Table 38 Median Changes in Pulse Rate- Treated Set

	E12.5+ M1000 bid	E12.5 + M500 bid	E5+ M1000 bid	E5 + M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Baseline								
Median	73.0	73.0	72.0	72.0	72.0	72.0	72.0	74.0
Q1, Q3	66.0, 80.0	67.0, 80.0	64.0, 79.0	64.0, 80.0	65.0, 78.0	64.0, 80.0	66.0, 78.0	68.0, 81.0
Week 24								
Median	72.5	73.0	72.0	72.0	72.0	71.0	74.0	73.0
Q1, Q3	68.0, 78.0	68.0, 80.0	68.0, 80.0	64.0, 79.0	65.0, 81.5	64.0, 77.0	67.0, 80.0	67.0, 79.0
Change from baseline								
Median	0.0	1.0	1.0	0.0	0.0	0.0	2.0	0.0
Q1, Q3	-6.0, 5.5	-5.0, 6.0	-5.0, 6.0	-5.0, 4.0	-4.0, 7.5	-6.0, 3.0	-4.0, 8.0	-6.0, 5.5

Source: Table 15.3.3:1 1276.1 Study Report Body

7.4.4 Electrocardiograms (ECGs)

12-lead ECG was performed on study day 1, and week 24. In addition to these visits, ECG was to be recorded in case of cardiac symptoms (indicating rhythm disorders or cardiac ischemia). All ECGs were evaluated (signed, dated and commented upon) by the treating physician/investigator and stored locally. Changes in ECG were to be recorded as an SAE in the eCRF, if judged clinically relevant by the investigator. No ECG changes were reported as AEs.

This study was not designed to assess the effect of empagliflozin on QT interval. Cardiovascular adverse events are discussed in section 7.3.5.1.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no evident dose dependency for adverse events based on review of the data from study 1276.1. See the previously completed reviews for the individual components for additional discussion of dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

No exploration for time dependency was performed.

7.5.3 Drug-Demographic Interactions

No detailed assessment of drug-demographic interaction was performed by the Applicant. Subgroup analyses by gender for UTI events, and genital infections are discussed in 7.3.5. Overall small numbers for subpopulations limits the value of subpopulation analyses. See previously completed reviews for the individual components for additional discussion of drug-demographic interaction for adverse events.

7.5.4 Drug-Disease Interactions

No specific exploration for drug-disease interaction was performed as part of this efficacy supplement. See the previously completed reviews for the individual components for additional discussion of drug-disease interactions for adverse events.

7.5.5 Drug-Drug Interactions

See the dedicated Clinical Pharmacology review for this efficacy supplement as well as the previously completed reviews for the individual components for detailed discussion of drug-drug interaction.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to section 7.3.5.9 for discussion on malignancies identified during this trial.

7.6.2 Human Reproduction and Pregnancy Data

No randomized data on use in pregnant or nursing women were collected as they were excluded from the study. There was one report of pregnancy occurring during study participation, in patient no (b) (6) a 25 year old female, in the E25 qd treatment group. The last recorded period was documented approximately 7 weeks after starting the study medication, which was prematurely discontinued approximately 10 weeks after starting it. The patient is reported to have given birth to 2 infants (one male, and one female) at 35 weeks gestation. No additional information is available.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable. No pediatric patients were enrolled in this study. Metformin is approved for use in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is little concern for overdose, drug abuse, withdrawal, or rebound.

8 Postmarket Experience

Both metformin and empagliflozin are FDA approved for the treatment of T2DM. Empagliflozin was approved on August 1, 2014, and metformin on March 3, 1995.The fixed dose combination product empagliflozin-metformin was recently approved on August 28, 2015.

On September 25, 2015, the Applicant submitted an annual report for Jardiance, covering the period between August 12, 2014, to June 6, 2015. The only clinical study ongoing/reporting for this time period is study 1245.25, a randomized, double-blind, placebo-controlled trial evaluating the effect of empagliflozin on the incidence of major adverse cardiovascular events in patients with type 2 diabetes (PMR 2755-4).

The FDA issued a drug safety communication on May 15, 2015 that sodium glucose cotransporter-2 (SGLT2) inhibitors may lead to (diabetic) ketoacidosis (DKA). The European Commission (EC) started a referral under Article 20 for SGLT2 inhibitors and the topic of DKA. FDA and EMA informed Boehringer Ingelheim about number of cases with DKA events with SGLT2 inhibitors. EMA requested marketing authorization holders (MAH) of SGLT2 inhibitors to provide details of the respective cases, including symptoms, patients at risk and diagnosis.

The applicant reported an analysis of BI data with the preferred terms (PT): Ketoacidosis, Diabetic Ketoacidosis, Acetonaemia was performed for a pool of randomized clinical trials (RCT) that investigated empagliflozin compared with placebo in patients with type 2 diabetes mellitus (T2DM). This analysis showed an overall low incidence of DKA in all treatment groups: 8 events consistent with DKA were reported in more than 12,000 patients with T2DM studied throughout phase 2 and phase 3 RCT. Reports in patients treated in the clinical trials were: empagliflozin 10 mg (2 events), empagliflozin 25 mg (1 event) and placebo (5 events).

Per Applicant report, the available data from post-marketing spontaneous reports observed from the current market exposure to Jardiance tablets was 13 cases (8 cases with T2DM as indication, 3 cases with unspecified indication and 2 cases during off-label use in type 1 diabetes mellitus (T1DM)) for Jardiance as of June 16, 2015, with a reporting rate of approximately 1 per 5000 patient years based on an estimated exposure of 66,052 patient years as of May 2015.

While the overall incidence of DKA with empagliflozin is low, it is consistent with what was observed postmarketing with the other two approved SGLT2i (canagliflozin, and dapagliflozin) which did have more post-marketing cases reported in the context of proportionally greater exposure.

In correspondence dated August 20, 2015, FDA notified BI that a new DARRTS Tracked Safety Issue (TSI) had been created for SGLT-2 inhibitors regarding urosepsis and fracture on August 18, 2015, which includes BI marketed products JARDIANCE and GLYXAMBI (and as of August 26, 2015, SYNJARDY).

Upon evaluation of clinical trials data and postmarketing reports, the FDA issued a Safety Labeling Change for all the approved SGLT2i to reflect the potential serious risk of DKA and urosepsis.

In correspondence dated August 20, 2015, FDA notified BI that a new DARRTS Tracked Safety Issue (TSI) had been created for SGLT2 inhibitors regarding stroke and thromboembolic events on June 18, 2015, which includes BI marketed products JARDIANCE and GLYXAMBI (and as of August 26, 2015, SYNJARDY).

During the reporting period for this Annual Report, the following required postmarketing reports for JARDIANCE tablets were submitted to NDA 204629:

- December 18, 2014: 6 months PBRER reporting from April 18, 2014 to October 17, 2014
- February 13, 2015: 3 month PADER reporting from October 18, 2014 to January 17, 2015
- June 25, 2015: 6 months PBRER reporting from October 18, 2014 to April 17, 2015
- August 12, 2015: 3 month PADER reporting from April 18, 2014 to July 17, 2015

Most reported AEs were consistent with the current prescribing information for empagliflozin (genital infections, worsening renal function, urinary tract infections etc.). It is notable that cases of ketoacidosis and urosepsis were reported, further supporting the FDA decision for a safety labeling change.

Though not identified in these submissions, there is ongoing internal discussion regarding the risk of fracture/decreases in bone mineral density due to a signal seen with another member in the class (canagliflozin).

9 Appendices

9.1 Labeling Recommendations

Labeling negotiations are ongoing at the time of completion of this review. The clinically relevant changes to the prescribing information for empagliflozin and empagliflozin-metformin fixed dose combination proposed by the Applicant are discussed below:

(b) (4)

(b) (4)

Section 14: The Applicant proposes to include the results of the study 1276.1, (b) (4)

In addition, the Applicant proposes the following change in indication for empagliflozin-metformin fixed dose combination product to "SYNJARDY is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and metformin, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin is appropriate". This change seems appropriate and supported by results of study 1276.1.

Because of the timing of the submission, the empagliflozin-metformin fixed dose combination label also complied with the PLLR rule, and sections 8.1-8.3 are under review by DPMH.

9.2 Financial Disclosures

Covered Clinical Study (Name and/or Number): 1276.1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 845		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 136		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

There were 136 investigators and sub-investigators that did not provide financial disclosure information. None of these investigators enrolled patients for this study, the reasons listed under not providing financial information are Site did not initiate/Did not participate as investigator

Only one investigator (b) (6) reported disclosable financial interests in the form of 2,381 shares and options of Eli Lilly with a value of $119,050 USD (Eli Lilly was a financial co-founder of the current study). This (b) (6) participated in site (b) (6) and (b) (6)

Overall, I do not feel that this information changes the validity of the study.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREEA O LUNGU
02/05/2016

WILLIAM H CHONG
02/08/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s005

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	204629 S005
Supporting document/s:	SN 0055/ SDN 0246
	SN 0026/ SDN 0027
Applicant's letter date:	05/20/15 (SN 0055)
	10/30/14 (SN 0026)
CDER stamp date:	05/20/15 (SN 0055)
	10/30/14 (SN 0026)
Product:	Empagliflozin
	(BI 10773)
Indication:	Type 2 Diabetes Mellitus
Applicant:	Boehringer Ingelheim Pharmaceuticals Inc.
Review Division:	DMEP
Reviewer:	Mukesh Summan, PhD, DABT
Supervisor/Team Leader:	Ron Wange, PhD
Division Director:	Jean-Marc Guettier, MD
Project Manager:	Michael White, PhD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204629 are owned by Boehringer Ingelheim Pharmaceuticals Inc., (BIPI) or are data for which BIPI has obtained a written right of reference. Any information or data necessary for approval of NDA 204629 that BIPI does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204629.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

NDA 204629 efficacy supplement 005 was submitted to the NDA under SDN 0055 to evaluate clinical study 1276.1. (b) (4)

1.2 Brief Discussion of Nonclinical Findings

Safety Pharmacology
The evaluation of empagliflozin in vitro safety pharmacology screens show empagliflozin to have low affinity binding suggestive of low potential for activity at the receptors, ion channels or transporters examined and for the human kinome.

PK/ADME
As expected the oral administration of radiolabeled empagliflozin in CD-1 mice showed the majority radioactivity to be distributed in the liver and kidney over the time. The exposure of empagliflozin relative to the blood was generally highest in the liver, followed by the kidney and lung, suggesting that highly perfused tissues are exposed to empagliflozin.

The active uptake of empagliflozin in rat and mouse kidney slices was predominantly by SGLT transporters followed by OAT3 transporters. The uptake into the rat and mouse kidney slices was concentration-dependent and saturable. Further in vitro characterization of empagliflozin in vesicular transport studies using xenopus laevis oocytes, showed empagliflozin to be a substrate of rat (Oat3, Oatp1a1), mouse (oatp1a1, oat3) and human SGLT2 transporters. The uptake of empagliflozin was time- and concentration-dependent, thus show active uptake of empagliflozin into the kidney.

In in vitro metabolism studies with mouse, rat and human kidney and liver microsomes, the most activity with regards to empagliflozin breakdown was with male mouse kidney microsomes. This metabolism predominantly formed metabolite M466/2. Furthermore, microsomes from the female kidney, mouse liver (male and female), rat liver (male and female), showed limited metabolism of empagliflozin to form metabolite M466/2. In contrast, incubation of empagliflozin with human liver microsomes did not result in the formation of metabolite M466/2, but yielded a glucuronide metabolite M626/1, which was also formed to a minimal extent with male mouse liver microsomes. Of note metabolite, M466/2 was formed at a 21-fold lower extent in the human kidney microsomes relative to male mouse kidney microsomes. These results suggest the formation of metabolite M466/2 in human kidneys is very minor relative to male mouse kidneys.

When evaluated in mouse kidney subcellular fractions (S9 and cytosol), M466/2 was also produced as a very minor metabolite thus suggesting oxidative metabolism in the microsomes primarily forms metabolite M466/2. Mouse kidney S9, cytosol, microsomes

alone or in combination also produced metabolites M688/1, M380/1 and M464/1, suggestive of further metabolites and down-stream processing of empagliflozin.

Metabolite M466/2 was found to stoichiometrically degrade to metabolite M380/1 (82%) in vitro and with minimal degradation to a 4-hydroxycrotoaldehyde metabolite that was trapped with glutathione (18%).

Treatment of CD-1 mice with a single dose of empagliflozin at 1000 mg/kg also identified metabolites M688/1, M380/1 and M464/1 as being formed by the kidneys in vivo. However, the male mouse kidney metabolized empagliflozin predominantly to metabolite M482/1 and at a 2-fold higher extent than the female mouse kidney. Metabolites M688/1, M380/1 and M464/1 were produced at 10-20% in male kidneys but less than 10% in the female mouse kidney, thus corroborating the in vitro gender differences in the kidney metabolism of empagliflozin.

Empagliflozin was shown to be not directly cytotoxic or mitogenic to mouse renal epithelial cells in vitro. In general, empagliflozin metabolites identified in vitro in the CD-1 mice were present to a much lower extent when mice were exposed to empagliflozin in vivo, Gender differences of metabolite formation were of particular note in male mouse kidney relative to the female mouse kidney. Metabolite M466/2 was also produced to much less extent in the mouse liver, rat liver, rat kidney and also the human liver and kidney. With regards to the human kidney, metabolite M466/2 was produced 21-fold lower relative to the male mouse kidney microsomes.

General Toxicology
Pivotal repeat dose studies were CD-1 mice treated with empagliflozin at 7 days and up to 13-weeks. The empagliflozin exposure was 6-153x MRHD (25 mg) in the 13-week mouse study.

Findings in the pivotal mouse studies were generally consistent with the pharmacodynamic activity of empagliflozin, including reduced body weight, glucosuria, polyuria, osmotic diuresis, electrolyte losses as has been previously described in this species. Of note urinary biomarkers clusterin, microalbumin, KIM-1 and MNGAL were increased, suggestive of renal injury. In addition, the enriched kidney cortex genomic analysis showed baseline (un-treated) gene expression differences in male and female CD-1 mice, in particular for metabolism enzymes and glutathione detoxification enzymes.

Genotoxicity
The empagliflozin metabolite M466/2 in a simulated Ames assay without the bacterial strains or metabolic activation showed the spontaneous degradation of M466/2 to metabolite M380/1, showing the very labile nature of M466/2. Evaluation of metabolite M466/2 in a standard in vitro Ames showed metabolite M466/2 was not mutagenic. However, metabolite M466/2 was found to induce micronuclei in the in vitro CHO cell assay at 24 hours post-dose without metabolic activation, with a dose-response effect. M466/2 is minimally formed in human kidney in vitro (21-lower compared to the mouse

kidney) and not observed in vivo, thus metabolite M466/2 is unlikely to be a risk to humans.

Computational structure activity relationship evaluation of metabolite M466/2 identified a structural alert(s) for metabolite M466/2. However, as metabolite M466/2 was negative in the AMES assay and showed equivocal findings in the in vitro micronucleus assay no further genotoxicity assessment is required.

Overall Summary

(b) (4)

(b) (4)

1.3 Recommendations

1.3.1 Approvability

NDA 204629 supplement 005 is approvable.

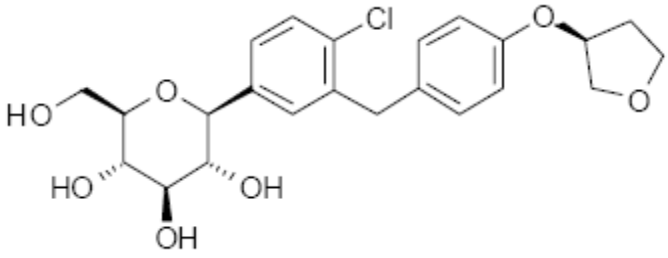
1.3.3 Labeling

The sponsor has revised (b) (4) of the label as follows:

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number	864070-44-0
Generic Name	Empagliflozin
Code Name	Jardiance™ / BI 10773 (BI 10773 XX)
Chemical Name	(1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3-yloxy]benzyl}phenyl)-D-glucitol
Molecular Formula/Molecular Weight	$C_{23}H_{27}ClO_7$ / 450.91 g/mol
Structure or Biochemical Description	
Pharmacologic Class	Sodium glucose co-transporter 2 (SGLT2) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 102145 (empagliflozin)
NDA 204629 (empagliflozin)

2.3 Drug Formulation

Empagliflozin is marketed as a 10 and 25 mg film-coated tablet with the following composition:

Active ingredient: 10 and 25 mg empagliflozin

Inactive ingredient: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Empagliflozin is indicated for treatment of Type 2 diabetes mellitus (T2DM). The recommended dose is 10 mg or 25 mg taken once daily.

2.7 Regulatory Background

The NDA for empagliflozin (NDA 204629) underwent a complete response (CR) 03.04.2014 and was subsequently approved 08.01.2014. The reason for the CR was unrelated to nonclinical toxicology. The nonclinical review of NDA 204629 was submitted to DARRTS 11.05.2013.

3 Studies Submitted

3.1 Studies Reviewed

Safety Pharmacology
Cerep In Vitro Pharmacology Screening Assays with Empagliflozin (BI 10773) and Comparator Compounds (Study# 13R085/Cerep 100006632, U13-3470-01, non-GLP)

SelectScreen® Biochemical Kinase Screening Assay With Empagliflozin (BI 10773) and Comparator Compounds (Study# 13R086, U13-3471-01, non-GLP)

Distribution

Quantitative Whole Body Autoradiography in Male and Female Albino Mice After a Single Oral Administration of [^{14}C]BI 10773 (Study# a073-12js, U13-1808-01, non-GLP)

In Vitro Evaluation of the Uptake of Empagliflozin into Kidney Slices from Male and Female Mouse and Rat (Study# PK1301T, U13-1840-02, non-GLP)

Metabolism

Investigations On the In Vitro Metabolism of [^{14}C]BI 10773 in Mouse, Rat and Human Kidney and Liver (Study# a337-131u, U13-1822-01, non-GLP)

In Vitro Evaluation of the Interaction of Empagliflozin with Mouse, Rat and Human SLC Transporters Using the Xenopus Oocyte System and HEK293 Cell System (Study# PK1304T, U13-1837-01, non-GLP)

BI 10773 XX Metabolite Profiling and Tentative Metabolite Identification in CD-1 Mouse Kidney (Study# DM-13-1002, U13-3477-02, non-GLP)

Bioanalysis of M466/2 (BI00737687) and M380/1, and Identification of the 4-hydroxycrotonaldehyde-GSH adduct from the degradation of M466/2 in Phosphate Buffer in the Presence of Glutathione (Study# DM-13-1129, U13-3897-01, non-GLP)

Toxicology

A 7 Day Renal Function and Toxicity Study with BI 10773 in CD-1 Mice (Study# 12R144, U13-3465-01, non-GLP)

A 13 Week Renal Pathogenesis Study with BI 10773 in CD-1 Mice (Study# 12R139, U13-3467-01, non-GLP)

Genotoxicity

Bacterial Reverse Mutation Assay (Study# U13-3656-01,13r096, non-GLP)

Bioanalysis of M466/2 (BI00737687) and M380/1 in Bacteria Reverse Mutation Assay Test Media Using Authentic Standard (Study# U13-3895-01)

In Vitro Mammalian Cell Micronucleus Screening Assay in Chinese Hamster Ovary (CHO) Cells Under Three Treatment Conditions (Study# 13R097, U13-3655-01, non-GLP)

Other Studies

In Vitro Studies With Empagliflozin (BI 10773) in Mouse Primary Renal Tubular Epithelial Cells (Study# 13R083, U13-3468-01, non-GLP)

Structure-Toxicity-Relationship Assessment of BI 10773 M466 Metabolites (Study# 13R084, U13-3469-01, non-GLP)

Genotoxicity of BI 10773? In Particular Genotoxicity of Male Mouse Predominant Metabolite M466(2) (Study# U13-3894-01, non-GLP) Expert Statement

3.2 Studies Not Reviewed

A 7 Day Renal Function and Toxicity Study with BI 10773 in Wistar-Hanover Rats (Study# 12R145, U13-3466-01, non-GLP)

Mode-of Action and Relevance for Empagliflozin-Related Renal Tumors in the Mouse Carcinogenicity Study (Study# U13-3693-02, non-GLP) SUMMARY DOCUMENT

3.3 Previous Reviews Referenced

The nonclinical review of NDA 204629 was submitted to DARRTS 11.05.2013.

4 Pharmacology

4.3 Safety Pharmacology

Cerep In Vitro Pharmacology Screening Assays with Empagliflozin (BI 10773) and Comparator Compounds (Study# 13R085/Cerep 100006632, U13-3470-01, non-GLP)

Method

In vitro pharmacology binding of BI 10773 (empagliflozin) and 8 other SGLTs inhibitors and 19 other non-SGLT2 small molecules including some nephrotoxicants were assessed using a Cerep screen (see sponsor's table below) . Empagliflozin was evaluated at 10 μM.

Table 1. Compounds Tested (sponsor's table)

Client Compound I.D.	Cerep Compound I.D.	General Name	Description with experimental carcinogenicity findings
Veronal	100006632-1	Veronal (barbital)	External drug, induces renal adenoma/carcinoma
BI0010773	100006632-2	Empagliflozin (BI 10773)	Internal SGLT2 inhibitor
EXRC3315BS	100006632-3	2-amino-4,5-diphenylthiazole	External compound, induces renal cystic changes
EXRS0647	100006632-4	Nitrofurantoin	External compound, acts through oxidative damage, induces nephropathy/renal tumors
BI00649737	100006632-5	Internal compound (Rho kinase inhibitor)	Internal discontinued compound, induces renal adenoma
EX00000381	100006632-6	8-Methoxypsoralen/Methoxsalen	External drug (photosensitizing agent), induces renal adenoma, carcinoma, associated nephropathy
EXRC3051XX	100006632-7	Phenolphthalein	External drug (laxative), induces renal adenoma/ carcinoma with associated nephropathy
DI00632140	100006632-8	Auranofin	External drug (gold-containing glucopyranoside), induces tubular karyomegaly, renal adenoma/carcinoma
EX00077721	100006632-10	Monuron	External compound, proximal tubule karyomegaly inducing renal carcinogen
BI00001475	100006632-11	Internal compound	Internal structurally dissimilar (to empagliflozin) active SGLT2 inhibitor
EXII0042XX	100006632-12	Tolcapone	External drug (COMT inhibitor), induces renal adenomas, adenocarcinomas
DI00002113	100006632-13	Phlorizin	External competitive inhibitor of SGLT1 and SGLT2
DI00632141	100006632-14	Methyleugenol	External compound, induces renal tubule hyperplasia and adenoma, associated nephropathy.
DI00632142	100006632-15	Tris(2-chloroethyl)phosphate	External compound believed to interact directly with DNA, induces tubular karyomegaly, hyperplasia and renal tumors
BI00014412	100006632-16	Internal compound	Internal structurally similar non-active SGLT2 inhibitor

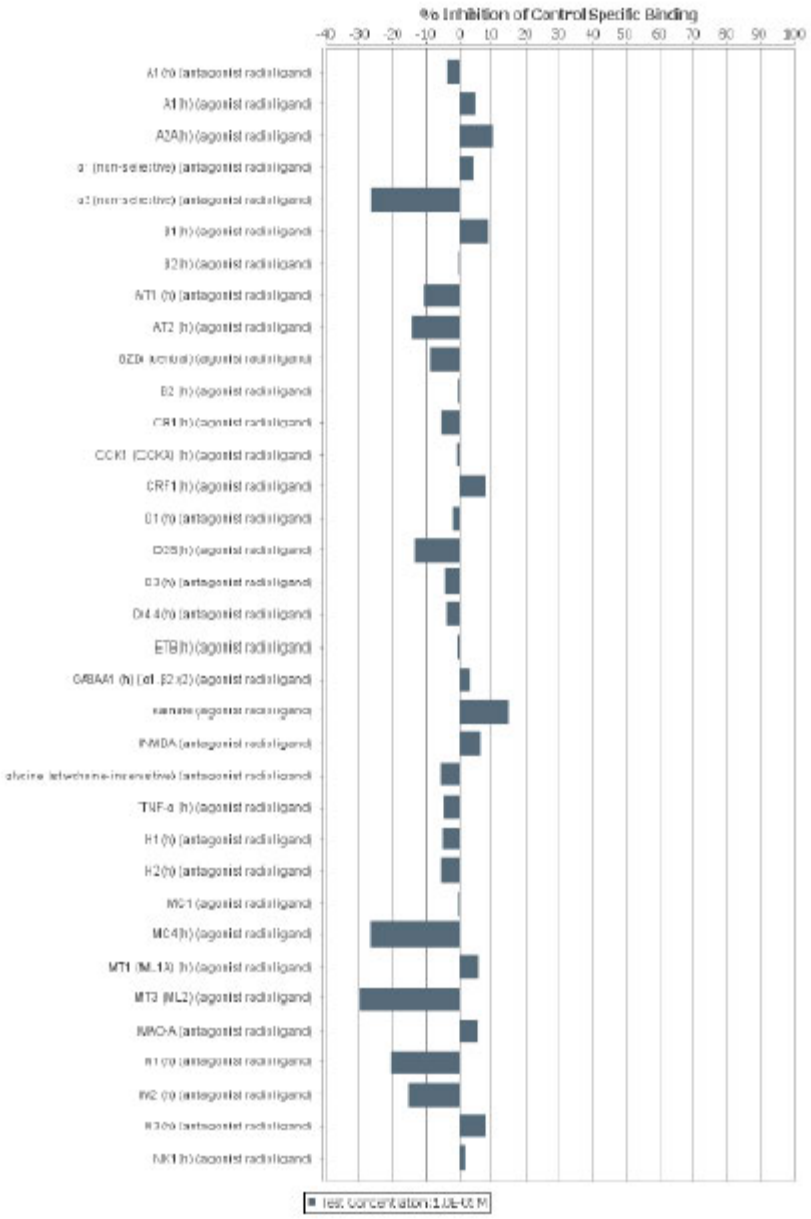
Table 1. Compounds Tested - continued (sponsor's table)

Client Compound I.D.	Cerep Compound I.D.	General Name	Description with experimental carcinogenicity findings
EX00002702	100006632-17	Ochratoxin A	External compound, induces renal adenoma/carcinoma, with associated renal cell necrosis, hyperplasia, cysts, karyomegaly
EX00003498	100006632-18	Entacapone	External drug (COMT inhibitor), induces renal adenomas and adenocarcinomas
EX00000047	100006632-19	Sergliflozin	External SGLT2 inhibitor
DI00632148	100006632-20	Remogliflozin	External SGLT2 inhibitor
DI00632147	100006632-21	Fumonisin B1	External compound, induces tubular hyperplasia, nephropathy and renal tumors (putatively acts through direct cytotoxicity and sustained tubular regeneration)
EX00001651	100006632-22	Ipragliflozin	External SGLT2 inhibitor
EX00000684	100006632-23	Dapagliflozin	External SGLT2 inhibitor
EX00001408	100006632-24	Tofogliflozin	External SGLT2 inhibitor
BI00010775	100006632-25	Internal compound	Internal structurally similar (to empagliflozin) active SGLT2 inhibitor
EX00001623	100006632-26	Canagliflozin	External SGLT2 inhibitor
EX00001671	100006632-27	External LX-4211 inactive	External inactive, structurally similar to LX-4211
EX00002041	100006632-28	External LX-4211	External dual SGLT1/SGLT2 inhibitor
DI00632149	100006632-9/29	Gentamicin	External compound, induces regenerative hyperplasia with acute tubular necrosis

Results

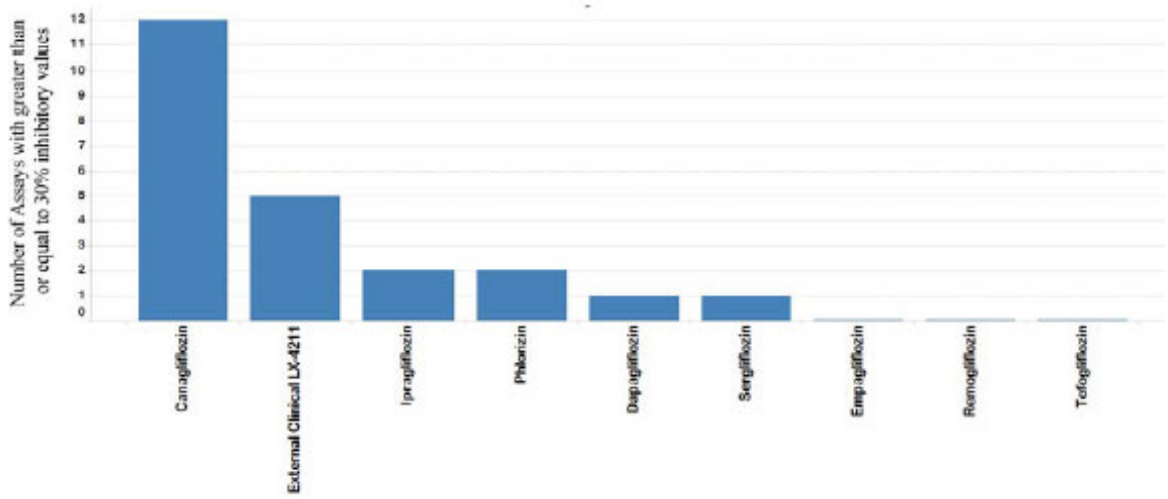
High affinity binding to receptors, ion channels or transporters was defined by the sponsor as ≥ 30% inhibition. High affinity binding was not observed with empagliflozin and empagliflozin was found to have a low affinity binding relative to the 8 other SGLT2 inhibitors that were assessed (see sponsor's figures below)

Figure 1. BI 10773 Binding in Cerep Screen at 10 μM (sponsor's figure)



Best possible image from Sponsor's submission.

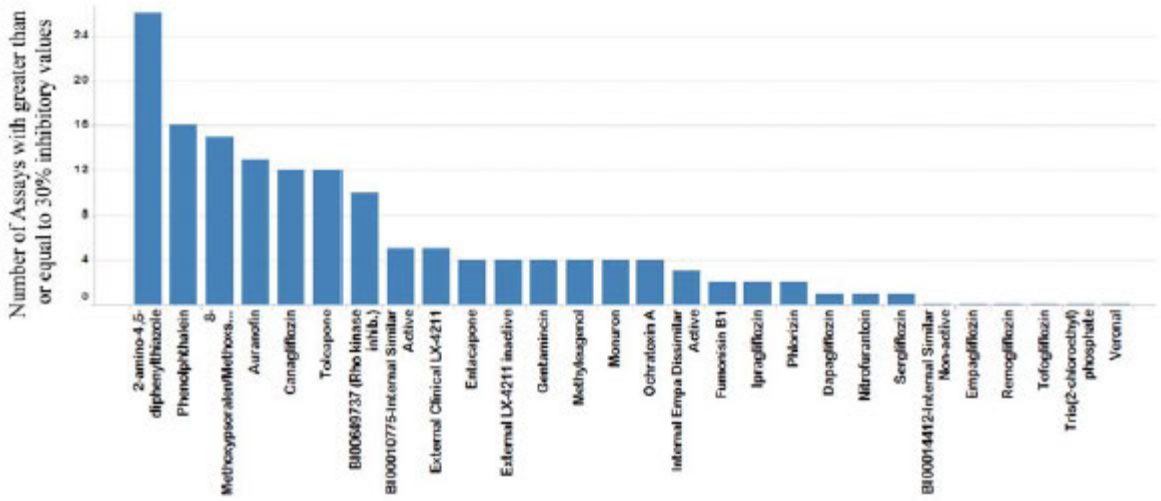
Figure 2. In Vitro binding of BI 10773 and Other SGLT2 Inhibitors As Assessed via Cerep Screen (sponsor's figure)



Best possible image from Sponsor's submission.

When compared to other NME's or nephrotoxicants, empagliflozin again minimally inhibited these assays (see sponsor's figure below)

Figure 3. In Vitro binding of BI 10773 and Other NME's as Assessed via Cerep Screen (sponsor's figure)



Best possible image from Sponsor's submission.

SelectScreen® Biochemical Kinase Screening Assay With Empagliflozin (BI 10773) and Comparator Compounds (Study# 13R086, U13-3471-01, non-GLP)

Method

The binding affinity of empagliflozin at 3 uM was assessed in an in vitro pharmacology panel of Invitrogen Life Technologies SelectScreen® biochemical kinase screening

(commercial) assay. Eight other SGLT2 inhibitors, non-SGLTs small molecules and nephrotoxicants were also assessed at 3 uM (see sponsor's table below).

Table 2. Compounds Tested in the Biochemical Kinase Assay (sponsor's table)

Client Compound I.D.	Compound I.D. (used by Invitrogen)	Compound Name	Description with experimental carcinogenicity findings (where applicable)
EXRC3051XX	376585	Phenolphthalein	External drug (laxative) with renal adenoma, carcinoma with associated nephropathy
EXRC3315BS	376984	2-amino-4,5-diphenylthiazole	External compound, induces renal cystic changes
EXII0042XX	386627	Tolcapone	External drug (COMT inhibitor) induces renal adenomas, adenocarcinomas
BI00014412	15014417	Internal compound	Internal structurally similar non-active SGLT2 inhibitor
EX00000047	15144655	Sergliflozin	External SGLT2 inhibitor
BI00649737	30135703	Internal compound (Rho kinase inhibitor)	Internal discontinued compound, induces renal adenoma
EX00000381	30256252	8-Methoxypsoralen/Methoxsalen	External drug (photosensitizing agent) with renal adenoma, carcinoma, associated nephropathy
DI00632140	30256255	Auranofin	External drug (gold-containing glucopyranoside), induces tubular karyomegaly, renal adenoma/carcinoma
DI00632141	30256258	Methyleugenol	External compound, induces renal tubule hyperplasia and adenoma, associated nephropathy
DI00632142	30256259	Tris(2-chloroethyl)phosphate	External compound believed to interact directly with DNA, induces tubular karyomegaly, hyperplasia and renal tumors
EXRS0647	30256260	Nitrofurantoin	External compound, acts through oxidative damage, induces nephropathy/renal tumors
EX00002702	30256261	Ochratoxin A	External compound, induces renal adenoma/carcinoma, with associated renal cell necrosis, hyperplasia, cysts, karyomegaly

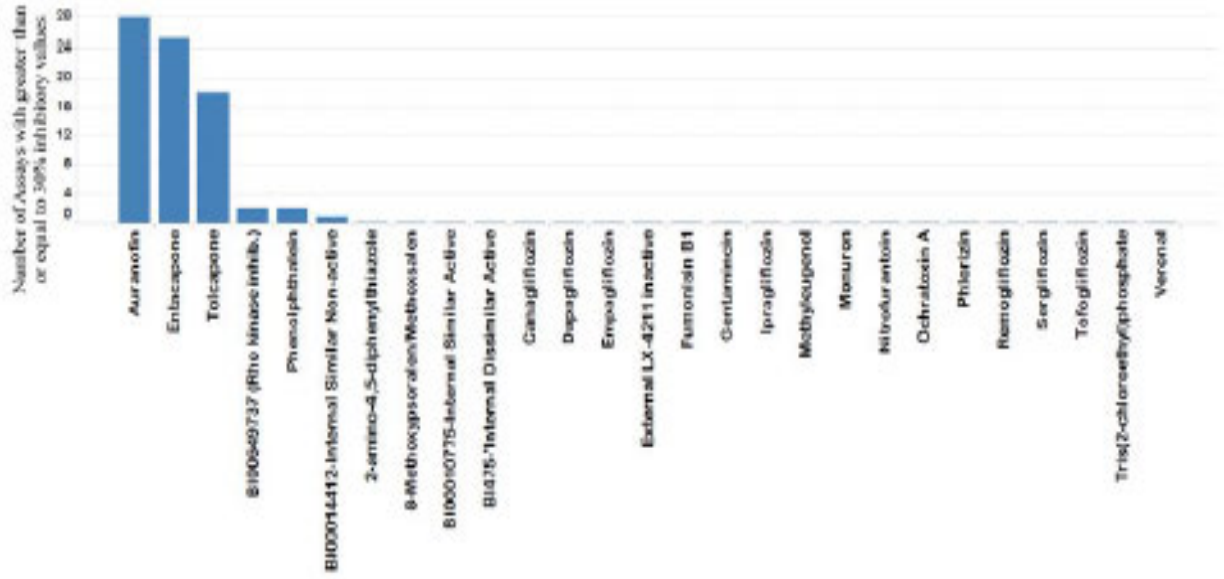
Table 2. Compounds Tested (sponsor's table) – continued

Client Compound I.D.	Compound I.D. (used by Invitrogen)	Compound Name	Description with experimental carcinogenicity findings (where applicable)
EX00077721	30256269	Monuron	External compound, proximal tubule karyomegaly inducing renal carcinogen
DI00002113	30256270	Phlorizin	External competitive inhibitor of SGLT1 and SGLT2
DI00632147	30256271	Fumonisin B1	External compound, induces tubular hyperplasia, nephropathy and renal tumors (putatively acts through direct cytotoxicity and sustained tubular regeneration)
DI00632148	30256272	Remogliflozin	External SGLT2 inhibitor
DI00632149	30256273	Gentamincin	External compound, induces regenerative hyperplasia with acute tubular necrosis
EX00003498	30256275	Entacapone	External drug (COMT inhibitor), induces renal adenomas and adenocarcinomas
BI00001475	15001480	Internal compound	Internal structurally dissimilar (to empagliflozin) active SGLT2 inhibitor
BI00010775	15010780	BI00010775-Internal Similar Active	Internal Similar Active to Empa
EX00001408	15935324	Tofogliflozin	External SGLT2 inhibitor
EX00001651	16071024	Ipragliflozin	External SGLT2 inhibitor
EX00001671	16081010	External LX-4211 inactive	External inactive, structurally similar to external dual SGLT1/SGLT2 inhibitor
EX00001623	CAN	Canagliflozin	External SGLT2 inhibitor
EX00000684	DAP	Dapagliflozin	External SGLT2 inhibitor
Veronal	Barbitol	Veronal	External drug, induces renal adenoma/carcinoma
BI0010773	BI0010773	Empagliflozin	Internal SGLT2 inhibitor

Results

Empagliflozin and the other SGLT2 inhibitors tested 3 uM, had low binding potential to the kinases and failed to inhibit the kinase panel at greater than 30% (see sponsor's figure below). Of note three of the nephrotoxicants evaluated in this assay, namely, entacapone, tolcapone and auranofin showed greater that 30% binding affinity in this assay (see sponsor's table below).

Figure 4. Inhibitory Ability of Empagliflozin in a subset of the Human Kinome (sponsor's figure)



Best possible image from Sponsor's submission.

Reviewer note: Entacapone (Comtan) and tolcapone (Tasmar) are catechol-o-methyl transferase (COMT) inhibitors. Both entacapone and tolcapone produce renal tumors and for tolcapone in particular, non-neoplastic degenerative renal changes in male and female rats were observed (renal tubularopathy, tubular hyperplasia and karyctomegaly) suggestive of a regenerative hyperplasia/neoplasia mechanism (per the pharmacology and toxicology review of NDA 20-796 for entacapone (Comtan) and NDA 20697 for tolcapone (Tasmar):
http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20796_Comtan.cfm

http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20697_Tasmar.cfm)

This suggests renal tumor formation may be a secondary change to chronic cell damage and cell repair. Furthermore, for tolcapone the major metabolites identified in humans and dogs are glucuronide metabolites and metabolism by the oxidative route to form a primary alcohol is predominant metabolite in rats. These COMT inhibitors uncannily show similar renal degeneration/regeneration and tumor findings that were observed in the male mouse kidney under chronic high exposures. However, despite these similarities the relevance of these findings to humans is not known.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Distribution

Quantitative Whole Body Autoradiography in Male and Female Albino Mice After a Single Oral Administration of [^{14}C]BI 10773 (Study# a073-12js, U13-1808-01, non-GLP)

Method

Male and female CD-1 mice (n=6/sex) were administered a single oral (gavage) treatment of [^{14}C]BI 10773 XX (aka empagliflozin) at 1,027 mg/kg. Tissue distribution of drug-related radioactivity was determined with radioluminography or liquid scintillation counting.

Results

At 1 hr the majority of radioactivity was in the liver, kidney and digestive tract for both male and female mice. This was followed by the cardiovascular system, circulatory system, endocrine system, respiratory system, locomotor system and integumentary system, respectively, (see sponsor's tables below). Low amounts of radioactivity were noted in the CNS.

Table 3. Tissue Distribution of A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Male Mice (sponsor's table)

organ system / tissue	time: 1 hour [µmol/kg]	4 hours [µmol/kg]	8 hours [µmol/kg]	12 hours [µmol/kg]
locomotor system				
muscle cranial	**188**	70.4	44.3	10.0
muscle caudal	**159**	70.4	35.3	9.41
bone marrow	**157**	48.9	30.2	6.15
digestive system				
tongue	**244**	81.4	66.8	13.9
salivary glands ♀	**254**	81.1	64.2	11.0
liver	**1,910**	843	553	133
pancreas	**353**	113	80.5	32.2
brown fat ♀	**122**	41.4	56.5	8.42
white fat ♀	**33.4**	12.2	7.01	1.30
respiratory system				
lung	**290**	273	81.7	40.0
cardiovascular system				
myocardium	**329**	95.3	79.6	16.2
spleen	**178**	45.6	41.2	8.99
thymus	106	**114**	28.2	7.16
urogenital system				
kidney (total)	**754**	367	265	74.2
renal cortex	**855**	437	333	98.4
renal outer medulla	**727**	286	191	61.4
renal inner medulla	**640**	462	248	34.4
testis	32.4	ND	**36.5**	7.38
epididymis	139	ND	ND	ND
vesicular gland	**77.5**	43.3	*3.71	6.39
preputial gland ♀	192	**194**	75.9	ND

Table 3. - Tissue Distribution of A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Male Mice –continued (sponsor's table)

organ system / tissue — time	1 hour [µmol/kg]	4 hours [µmol/kg]	8 hours [µmol/kg]	12 hours [µmol/kg]
endocrine system				
adrenal (total)	ND	ND	62.7	10.6
adrenal cortex	**261**	87.0	62.4	8.80
adrenal medulla	**204**	71.5	51.1	13.5
pituitary gland (hypophysis) φ	**214**	78.5	79.4	7.86
central nervous system				
brain (total)	**9.22**	6.68	*3.33	BLD
pros- & mesencephalon	**8.59**	6.81	*3.67	BLD
rhombencephalon	**10.6**	4.96	BLD	BLD
sensory system (visual)				
total eyeball (LSC)	**57.3**	26.7	18.6	3.17
Harderian gland	**322**	148	83.4	21.2
integumentary system				
skin (total)	**125**	70.1	38.9	6.40
circulatory system				
whole blood (LSC)	**307**	116	39.0	18.3

file: OW_A073_12JS_02.xls
asterisk (*)= value between LLOQ and LOD
BLD= below limit of detection
ND= organ/tissue not detected
phi (φ)= potentially underestimated due to minute size, difficult delimitation or elevated self-absorption
psi (ψ)= mostly submandibular gland, partly parotid or sublingual gland

Table 4. Tissue Distribution of A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Female Mice (sponsor's table)

organ system / tissue	time	1 hour *[µmol/kg]*	4 hours *[µmol/kg]*	8 hours *[µmol/kg]*	12 hours *[µmol/kg]*
locomotor system					
muscle cranial		**233**	67.1	23.3	11.3
muscle caudal		**193**	68.5	19.6	10.3
bone marrow		**192**	39.4	16.2	4.45
digestive system					
tongue		**312**	ND	30.5	10.5
salivary glands ψ		**297**	76.6	24.9	19.0
liver		**2,170**	685	350	89.2
pancreas		**432**	115	53.0	18.8
brown fat ♀		**153**	33.3	22.7	7.74
white fat ♀		**116**	68.0	5.36	8.10
respiratory system					
lung		**430**	145	75.3	56.3
cardiovascular system					
myocardium		**442**	97.7	40.2	12.0
spleen		**204**	53.7	21.8	5.27
thymus		**133**	52.0	18.9	7.45
urogenital system					
kidney (total)		ND	302	176	67.8
renal cortex		**1,100**	270	159	75.2
renal outer medulla		**985**	306	193	73.4
renal inner medulla		**1,200**	408	131	31.2
clitoral gland ♀		323	ND	ND	ND

Table 4. - Tissue Distribution of A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Female Mice - continued (sponsor's table)

organ system / tissue — time	1 hour *[µmol/kg]*	4 hours *[µmol/kg]*	8 hours *[µmol/kg]*	12 hours *[µmol/kg]*
endocrine system				
adrenal (total)	**318**	53.1	ND	7.31
adrenal cortex	**310**	44.2	41.8	6.49
adrenal medulla	**289**	56.8	42.9	4.46
pituitary gland (hypophysis) φ	**283**	75.0	34.9	BLD
central nervous system				
brain (total)	**8.61**	5.76	BLD	BLD
pros- & mesencephalon	**8.71**	5.51	BLD	BLD
rhombencephalon	**10.2**	5.48	BLD	BLD
sensory system (visual)				
total eyeball (LSC)	**72.1**	18.3	6.92	4.04
Harderian gland	**358**	141	65.9	39.1
integumentary system				
skin (total)	**162**	50.0	21.8	8.85
circulatory system				
whole blood (LSC)	**422**	80.1	74.2	8.30

file: OW_A073_12JS_02.xls
BLD= below limit of detection
ND= organ/tissue not detected
phi (φ)= potentially underestimated due to minute size, difficult delimitation or elevated self-absorption
psi (ψ)= mostly submandibular gland, partly parotid or sublingual gland

The same tissues as described above showed the highest radioactivity at the 4, 8 and 12 hour time points in both males and females, as exemplified by the sponsor's figures below; and the radioactivity gradually decreased (see sponsor's tables above).

Figure 5. Time Course of Tissue Distribution of A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Male Mice (sponsor's figure)

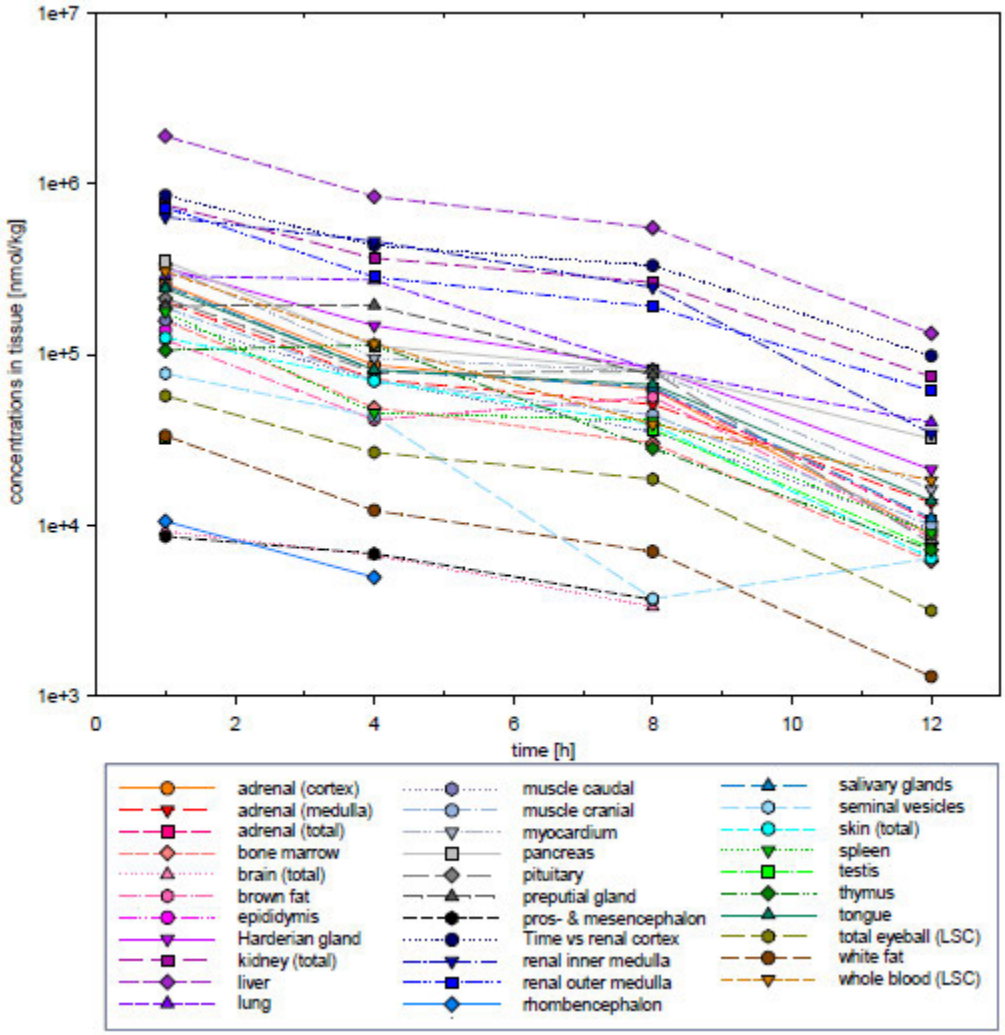
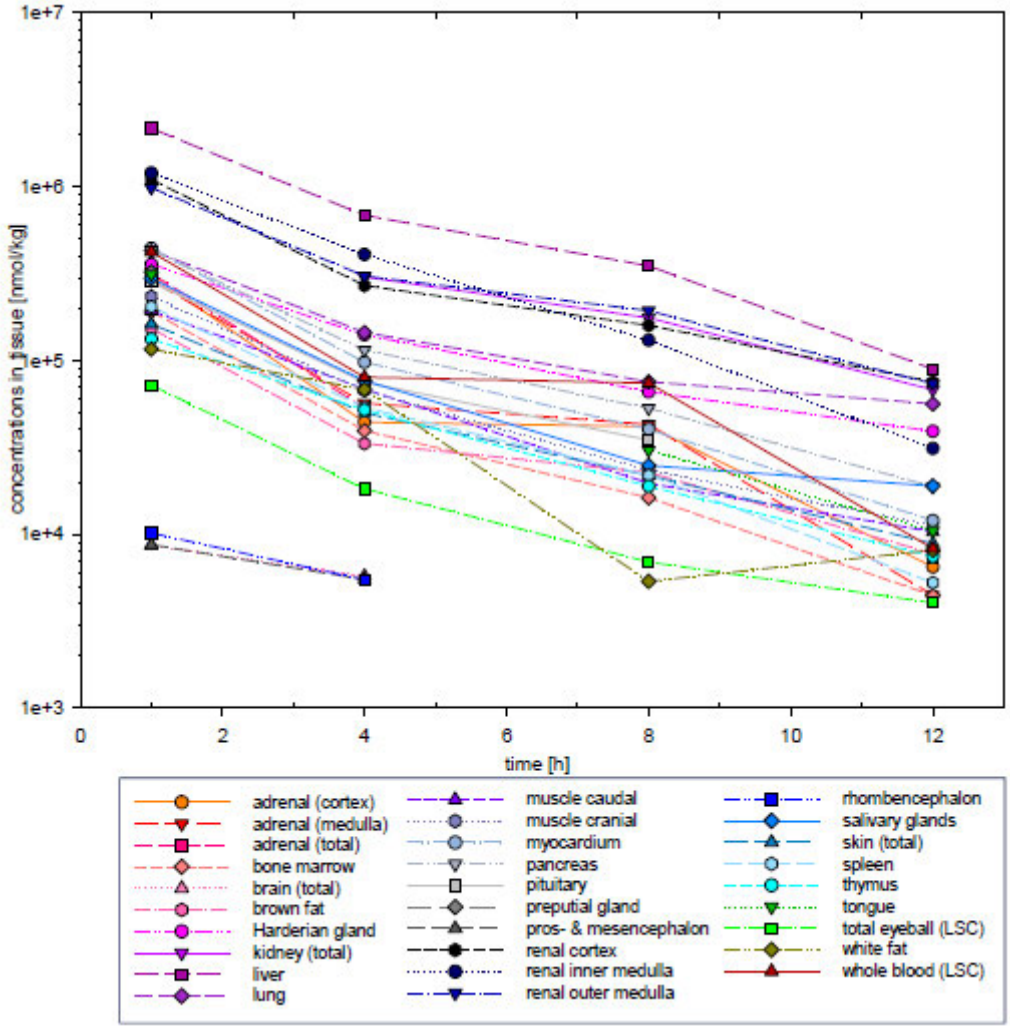


Figure 6. Time Course of Tissue Distribution of A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Female Mice (sponsor's figure)



Exposure in terms of $AUC_{(0\text{-}12h)}$ relative to the blood was generally highest in the liver, followed by the kidney and lung (see sponsor's table below). Half-life in tissues was generally 2-3 hrs.

Table 5. PK Parameters For A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Male Mice (sponsor's table)

organ system / tissue	parameter [unit]	t(1/2) [h]	time interval	R^2	AUC(0-12h) [(µmol·h)/L]
locomotor system					
muscle cranial		2.8	1-12 [h]	0.96	771
muscle caudal		2.8	1-12 [h]	0.98	687
bone marrow		2.5	1-12 [h]	0.96	573
digestive system					
tongue		2.9	1-12 [h]	0.92	997
salivary glands ♀		2.7	1-12 [h]	0.92	991
liver		3.1	1-12 [h]	0.96	8,800
pancreas		3.5	1-12 [h]	0.94	1,400
brown fat ♀		3.0	1-12 [h]	0.98	580
white fat ♀		2.5	1-12 [h]	0.96	131
respiratory system					
lung		3.5	1-12 [h]	0.94	1,860
cardiovascular system					
myocardium		2.8	1-12 [h]	0.92	1,240
spleen		2.9	1-12 [h]	0.90	638
thymus		2.7	1-12 [h]	0.92	690
urogenital system					
kidney (total)		3.5	1-12 [h]	0.95	3,840
renal cortex		3.8	1-12 [h]	0.94	4,590
renal outer medulla		3.3	1-12 [h]	0.97	3,180
renal inner medulla		2.5	1-12 [h]	0.97	3,770
testis		†5.2	1-12 [h]	1.00	330
epididymis		NC	NC	NC	NC
vesicular gland		*3.0	1-12 [h]	1.00	*299
preputial gland ♀		5.0	1-8 [h]	0.81	NC

Table 5. PK Parameters For A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Male Mice - continued (sponsor's table)

organ system / tissue	parameter [unit]	t(1/2) [h]	time interval	R^2	AUC(0-12h) [(µmol·h)/L]
endocrine system					
adrenal (total)		NC	NC	NC	368
adrenal cortex		2.4	1-12 [h]	0.93	1,010
adrenal medulla		3.0	1-12 [h]	0.95	838
pituitary gland (hypophysis) φ		2.3	1-12 [h]	1.00	951
central nervous system					
brain (total)		*4.7	1-8 [h]	0.98	NC
pros- & mesencephalon		*5.6	1-8 [h]	0.97	NC
rhombencephalon		NC	NC	NC	NC
sensory system (visual)					
total eyeball (LSC)		2.8	1-12 [h]	0.92	274
Harderian gland		2.9	1-12 [h]	0.97	1,470
integumentary system					
skin (total)		2.7	1-12 [h]	0.93	632
circulatory system					
whole blood (LSC)		2.7	1-12 [h]	0.99	1,130

file: OW_A073_12JS_Toxkin.xls
asterisk (*)= calculation based on value between LLOQ and LOD
dagger (†)= unreliable value (time interval for determination < 2×t(1/2 or λ(z) based on 2 points in time only)
NC= not calculated
phi (φ)= potentially underestimated due to minute size, difficult delimitation or elevated self-absorption
psi (ψ)= mostly submandibular gland, partly parotid or sublingual gland

Table 6. PK Parameters For A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Female Mice (sponsor's table)

organ system / tissue	parameter [unit]	t(1/2) [h]	time interval	R^2	AUC(0-12h) [(µmol·h)/L]
locomotor system					
muscle cranial		2.6	1-12 [h]	0.97	749
muscle caudal		2.6	1-12 [h]	0.98	671
bone marrow		2.1	1-12 [h]	0.97	526
digestive system					
tongue		2.2	1-12 [h]	1.00	1,080
salivary glands ♂		2.8	1-12 [h]	0.90	907
liver		2.5	1-12 [h]	0.98	7,700
pancreas		2.6	1-12 [h]	0.97	1,390
brown fat ♀		2.8	1-12 [h]	0.93	478
white fat ♀		2.8	1-12 [h]	0.99	453
respiratory system					
lung		3.9	1-12 [h]	0.90	1,690
cardiovascular system					
myocardium		2.2	1-12 [h]	0.98	1,260
spleen		2.2	1-12 [h]	0.99	628
thymus		2.7	1-12 [h]	1.00	505
urogenital system					
kidney (total)		3.7	4-12 [h]	0.98	1,990
renal cortex		3.1	1-12 [h]	0.93	3,610
renal outer medulla		3.2	1-12 [h]	0.96	3,710
renal inner medulla		2.1	1-12 [h]	1.00	4,050
clitoral gland ♀		NC	NC	NC	NC

Table 6. PK Parameters For A Single 1027 mg/kg Dose of [^{14}C] BI 10773 in Female Mice - continued (sponsor's table)

organ system / tissue	parameter [unit]	t(1/2) [h]	time interval	R^2	AUC(0-12h) [(µmol·h)/L]
endocrine system					
adrenal (total)		2.1	1-12 [h]	0.95	787
adrenal cortex		2.1	1-12 [h]	0.93	812
adrenal medulla		1.9	1-12 [h]	0.98	839
pituitary gland (hypophysis) φ		2.4	1-8 [h]	0.95	NC
central nervous system					
brain (total)		†5.2	1-4 [h]	1.00	NC
pros- & mesencephalon		†4.5	1-4 [h]	1.00	NC
rhombencephalon		†3.4	1-4 [h]	1.00	NC
sensory system (visual)					
total eyeball (LSC)		2.7	1-12 [h]	0.94	222
Harderian gland		3.5	1-12 [h]	0.97	1,480
integumentary system					
skin (total)		2.7	1-12 [h]	0.98	560
circulatory system					
whole blood (LSC)		2.0	1-12 [h]	0.97	1,260

file: OW_A073_12JS_Toxkin.xls
dagger (†)= unreliable value (time interval for determination < 2×t(1/2) or λ(z) based on 2 points in time only)
NC= not calculated
phi (φ)= potentially underestimated due to minute size, difficult delimitation or elevated self-absorption
psi (ψ)= mostly submandibular gland, partly parotid or sublingual gland

In Vitro Evaluation of the Uptake of Empagliflozin into Kidney Slices from Male and Female Mouse and Rat (Study# PK1301T, U13-1840-02, non-GLP)

Method

Kidney slices from male and female mice (CD-1 mice, 11 weeks old) and rats (WI (Han) rats, 9-10 weeks old) were used to determine the transport capacity of empagliflozin/ [^{14}C]empagliflozin or reference transporter substrate/inhibitor compounds [transporter probe substrates: benzylpenicillin (PCG)/benzyl [^{14}C]-penicillin, methyl-α-D-glucopyranoside (α MG)/[glucose-^{14}C (U)]- (α MG); [1-^{14}C]-D-mannitol; inhibitor substrates: probenecid (PB) and phlorizin (PZ)]. Radioactivity was determined with liquid scintillation counting. One kidney slice incubation was composed of three kidney slices from three different animals. The uptake of transporter probe substrates and inhibitors was evaluated under time or concentration as described in the following sponsor's table:

Table 7. Experimental Conditions (sponsor's table)

Experimental design	Incubation time (min)	Empagliflozin concentration (µM)	Inhibitor and concentration (µM)
Time dependency	5, 15 and 30	10 and 1000	None
Concentration dependency	15	0.1, 1, 10, 30, 100, 300 and 1000	None
Effect of prototypical inhibitor	15	0.1 and 1000	PB (100) PZ (10)

Results

The uptake of PCG which is a probe substrate of OAT3 and expressed on the basolateral membrane, and αMG a probe substrate of SGLT's and expressed on the brush border membrane, were demonstrated in rat and mouse kidney slices (see sponsor's figure below). In addition, PB showed inhibition of the rat and mouse kidney OAT3 transporter and PZ showed inhibition of the mouse and rat kidney SGLT transporters (see sponsor's figure below). The use of high concentrations of PCG and αMG resulted in lower OAT3 and SGLT transport, respectively, suggesting that the transport is an active process that may be saturated.

Figure 7. Uptake of PCG in Rat and Mouse Kidney Slices (sponsor's figure)

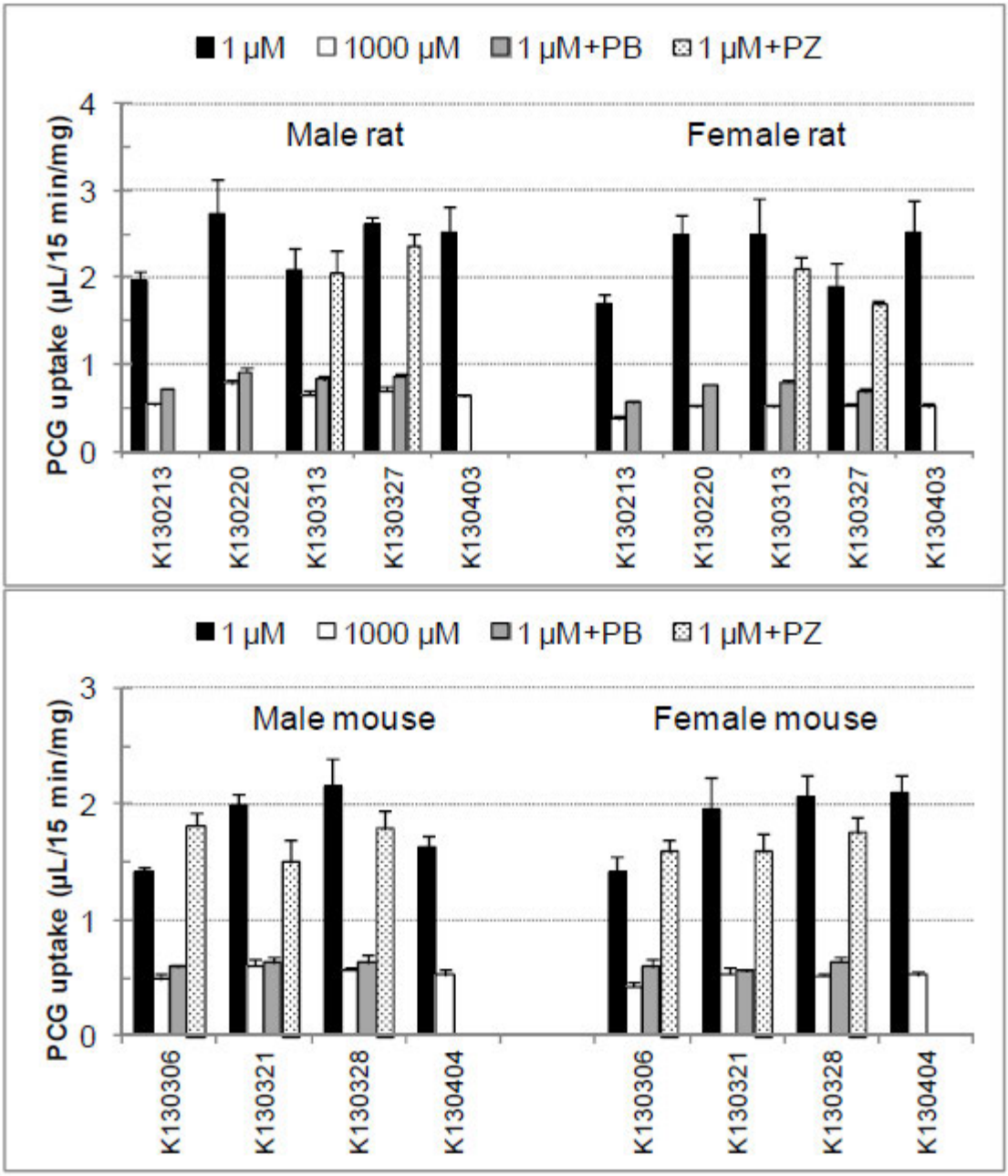
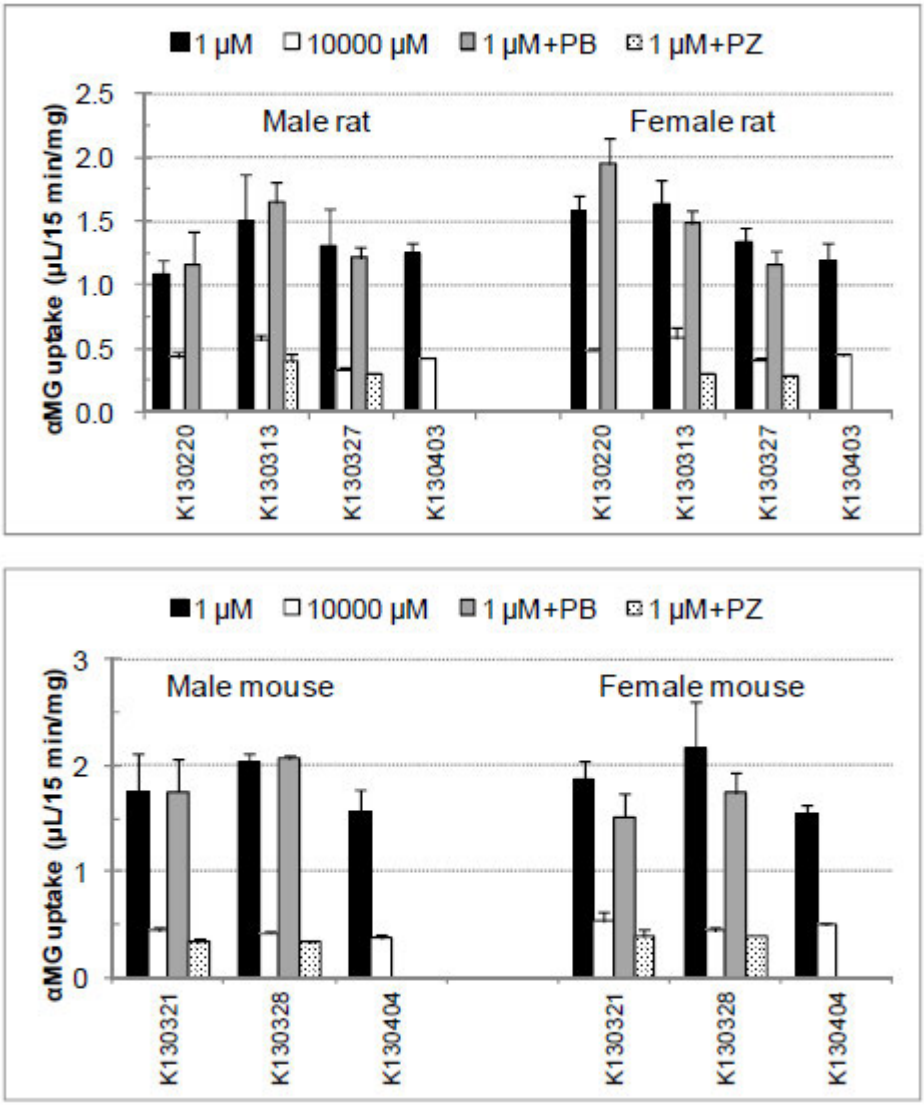
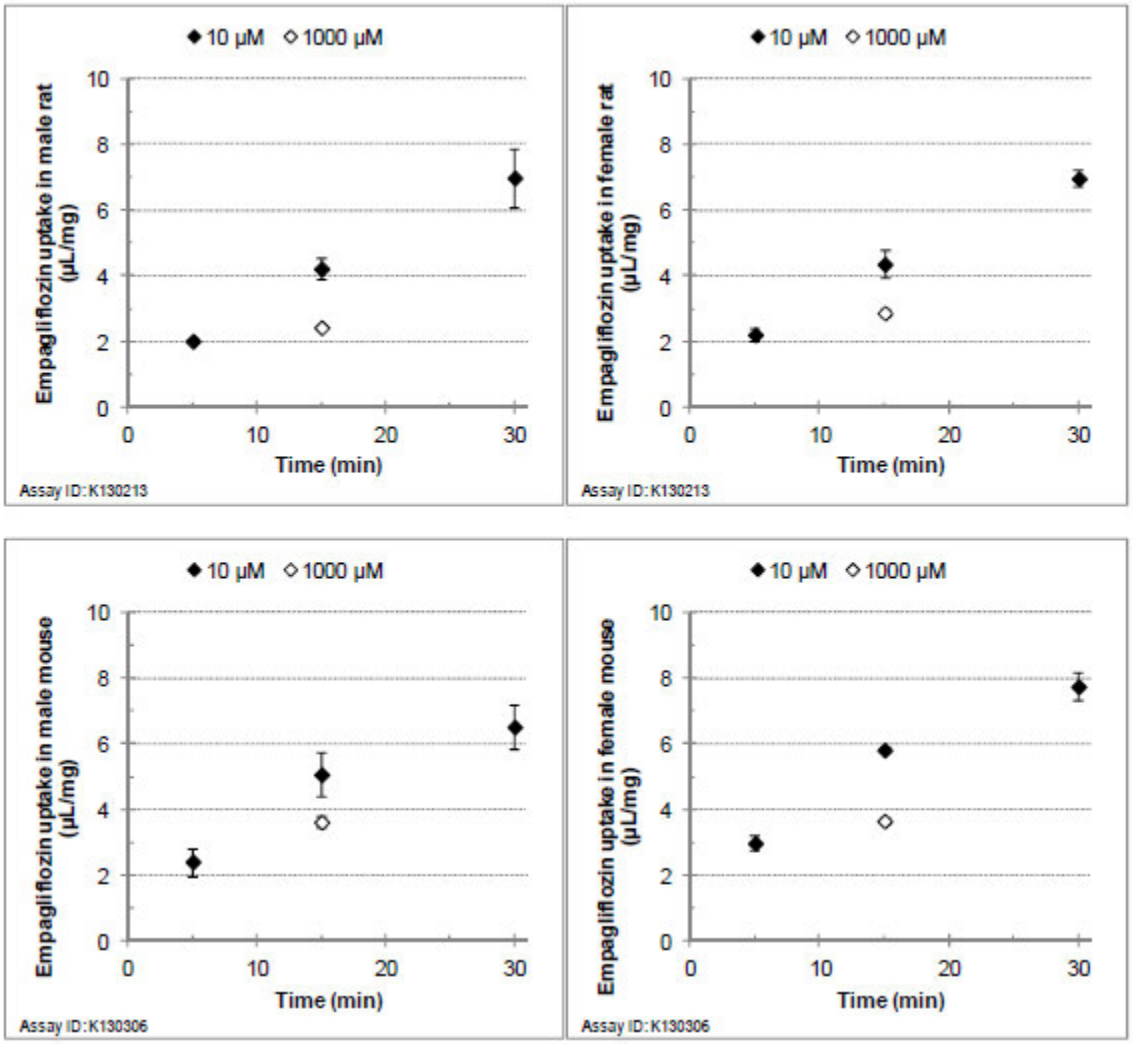


Figure 8. Uptake of αMG in Rat and Mouse Kidney Slices (sponsor's figure)



Uptake of empagliflozin was demonstrated in both the rat and mouse kidney slices and showed a time dependent increase in both species and was independent of sex. The high concentrations of empagliflozin showed lower SGLT transport, suggesting that the transport is an active process that may be saturated (see sponsor's figure below).

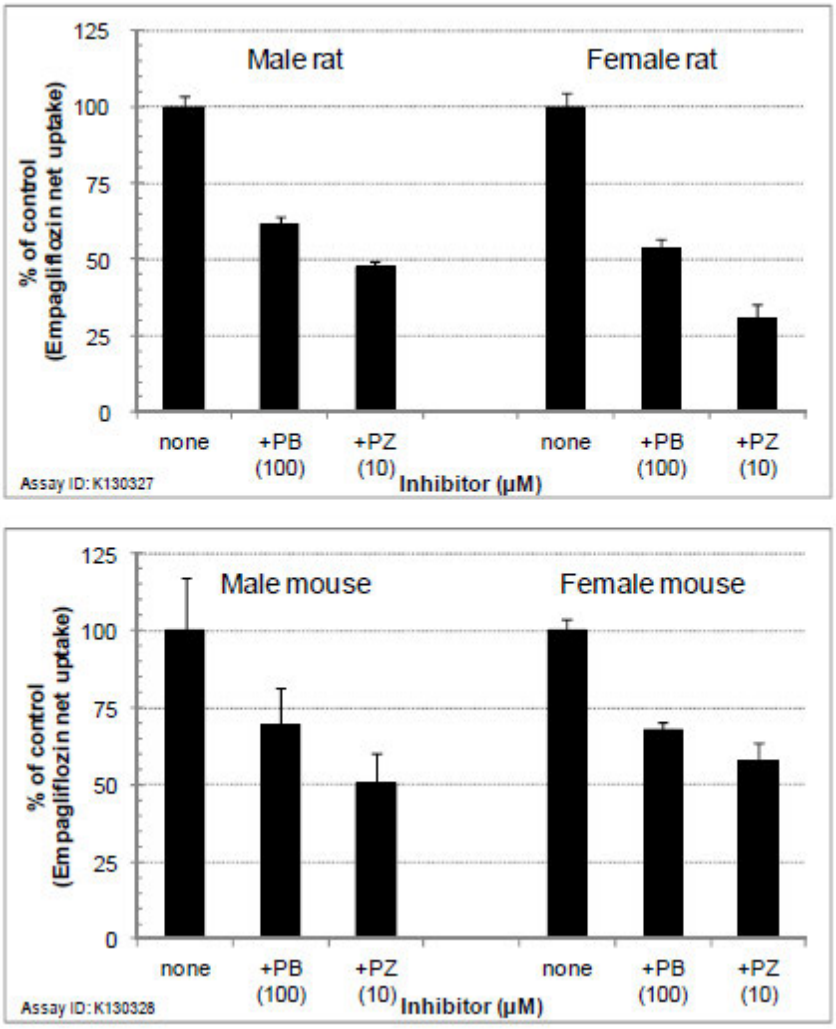
Figure 9. Uptake of Empagliflozin in Rat# and Mouse^ Kidney Slices (sponsor's figure)



#Rat: Top Panels, Male Left Panel and Female Right Panel.
^Mouse: Bottom Panels, Male Left Panel and Female Right Panel.

The uptake of empagliflozin was inhibited predominantly by PZ and also by PB in both the rat and mouse kidney slices and was not gender specific (see sponsor's figure below). This suggests that SGLT's are primarily responsible for the transport of empagliflozin, followed by OAT3 transporters (see sponsor's table below).

Figure 10. Uptake and Inhibition of Empagliflozin in Rat# and Mouse^ Kidney Slices (sponsor's figure)



#Rat: Top Panels, Male Left Panel and Female Right Panel.
^Mouse: Bottom Panels, Male Left Panel and Female Right Panel.

Table 8. Uptake and Inhibition of Empagliflozin in Rat and Mouse Kidney Slices (sponsor's table)

Assay ID: K130327 / Empagliflozin uptake												
Empagliflozin concentration (μM)	Inhibitor (μM)	Uptake (μL/15 min/mg)				Net uptake (μL/15 min/mg)				% of control (net uptake)			
		Male rat		Female rat		Male rat		Female rat		Male rat		Female rat	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.1	none	6.67	0.272	5.96	0.173	3.80	0.336	2.92	0.260	100	3.29	100	4.31
0.1	Probenecid (100)	5.22	0.226	4.61	0.0489	2.35	0.300	1.57	0.200	61.8	2.53	53.8	2.86
0.1	Phlorizin (10)	4.67	0.160	3.94	0.318	1.80	0.254	0.900	0.373	47.4	2.08	30.8	4.47
1000	none	2.87	0.197	3.04	0.194	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Assay ID: K130328 / Empagliflozin uptake													
Empagliflozin concentration (μM)	Inhibitor (μM)	Uptake (μL/15 min/mg)				Net uptake (μL/15 min/mg)				% of control (net uptake)			
		Male mouse		Female mouse		Male mouse		Female mouse		Male mouse		Female mouse	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.1	none	8.85	1.64	8.10	0.381	4.09	2.04	3.75	0.383	100	17.2	100	3.85
0.1	Probenecid (100)	7.61	0.653	6.88	0.278	2.85	1.37	2.53	0.280	69.7	11.8	67.5	2.71
0.1	Phlorizin (10)	6.82	0.302	6.51	0.792	2.06	1.25	2.16	0.793	50.4	9.67	57.6	5.85
1000	none	4.76	1.21	4.35	0.0369	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

In Vitro Evaluation of the Interaction of Empagliflozin with Mouse, Rat and Human SLC Transporters Using the Xenopus Oocyte System and HEK293 Cell System (Study# PK1304T, U13-1837-01, non-GLP)

Method

The sponsor used the following hierarchy for distinguishing mouse (lower case), rat (1st letter upper case) and human (all caps) for identifying transporters e.g. sglt2 (mouse) Sglt2 (rat) and SGLT2 (human).

Stably transfected *Xenopus laevis* oocytes cells expressing mouse or rat solute carrier transporters: (SLC) oat1/Oat1, oat3/Oat3, oct1/Oct1, oct2/Oct2, oatp1a1/Oatp1a1, sglt1/Sglt1 or sglt2/Sglt2, respectively, were used to determine the transport capacity of these transporters for [^{14}C]empagliflozin/empagliflozin. Reference transporter substrate/inhibitor compounds (see sponsor's table below) were used as positive controls. Stably transfected (human embryonic kidney) HEK-293 cells expressing human SGLT1 or SGLT2 were also used to determine the transport capacity of these cells to transport[^{14}C]empagliflozin/empagliflozin or reference transporter substrate/inhibitor compounds (see sponsor's table below). Selectivity of each prototypical transport inhibitor is shown in the sponsor's table below. Radioactivity was determined with liquid scintillation counting.

Table 9. Summary of Reference Transporter Probe Substrate or Inhibitor for Each Transporter (sponsor's table)

Isoform	Probe substrate (μM)	Typical inhibitor (μM)
oat1/Oat1	[^{3}H]PAH (1)	Probenecid (100)
oat3/Oat3	[^{3}H]E-sul (0.1)	Probenecid (100)
oct1/Oct1	[^{3}H]MPP$^+$ (1)	Cimetidine (1000)
oct2/Oct2	[^{3}H]MPP$^+$ (1)	Cimetidine (1000)
oatp1a1/Oatp1a1	[^{3}H]$E_2$17βG (0.1)	Rifampicin (600)
sglt1/Sglt1/SGLT1	[^{14}C]αMG (20)	Phlorizin (10 or 100)
sglt2/Sglt2/SGLT2	[^{14}C]αMG (20)	Phlorizin (10 or 100)

Table 10. Selectivity of Reference Transporter Inhibitors for Each Transporter (sponsor's table)

	SGLT2	sglt1/Sglt1/SGLT1	oatp1a1/Oatp1a1	oat3/Oat3
Probenecid (100 μM)	*	* (mouse) ** (rat)	*** (mouse/rat)	**** (mouse/rat)
Rifampicin (600 μM)	ND	** (mouse/rat)	**** (mouse) ***(rat)	*(mouse) ** (rat)
Phlorizin (10 μM)	****	**** (mouse/rat)	*(mouse) ND (rat)	** (mouse/rat)
Phlorizin (100 μM)	****	**** (mouse/rat)	**(mouse) ND(rat)	*** (mouse/rat)

****: Complete inhibition (100-80%); ***: Moderate inhibition (80-50%); **: Weak inhibition (50-20%); *: No inhibition (20-0%); ND: not done

Results

Xenopus laevis oocytes failed to transport the sglt2/Sglt2 and SGLT2 probe substrate methyl α-D-glucopyranoside (α-MG), suggesting the presence of a non-functional transporter (data not shown).

Empagliflozin was found to be a concentration-dependent substrate for rat Oat3 and mouse oatp1a1 and oat3 (see Sponsor's figure below). Empagliflozin was also found to be a substrate for rat Oatp1a1, Oat3 and mouse oatp1a1 and oat3, respectively, with increase in uptake by increasing the oocyte cRNA for each transporter, and corresponding inhibition of empagliflozin transport with the prototypical inhibitor (see sponsor's figure below).

Figure 11. Empagliflozin Uptake at 1 – 1000 uM in Oocytes Injected with oatp1a1 (left), Oat3 or oat3 (right) or Water (sponsor's figure)

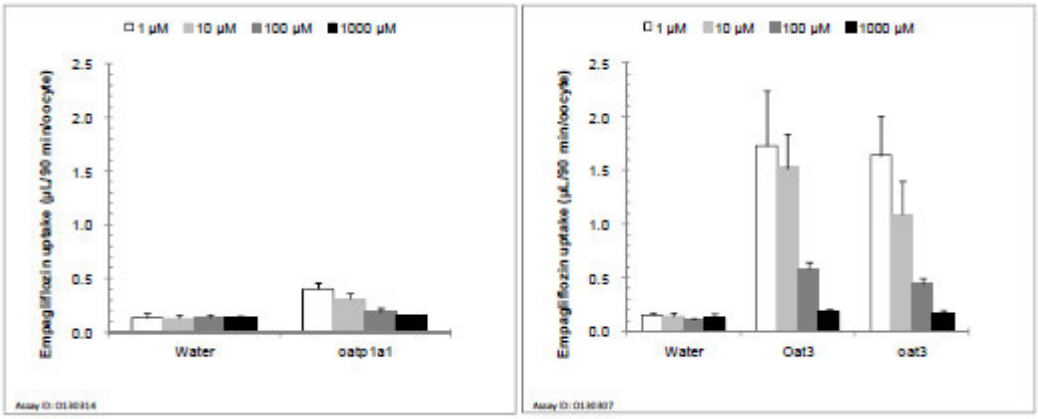
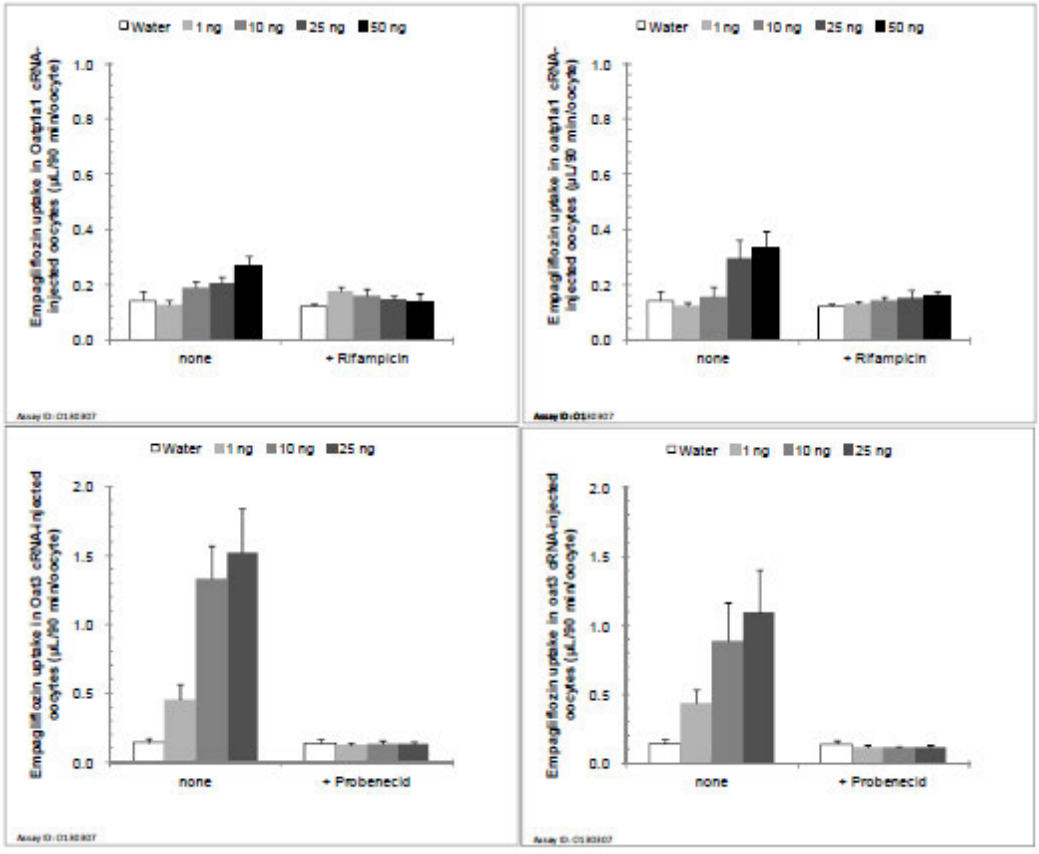
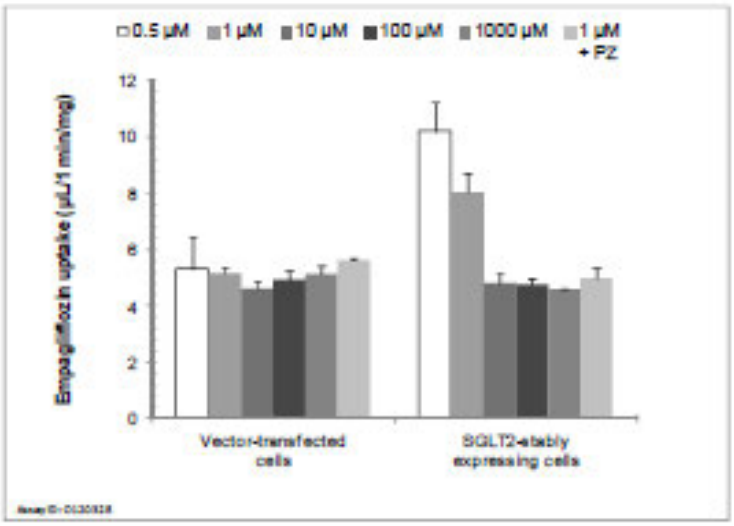


Figure 12. Empagliflozin Uptake in Oocytes Injected with 1-50 ng cRNA for Oatp1a1 (top left), oatp1a1 (top right), Oat3 (bottom left) or oat3 (bottom right) or Water (sponsor's figure)



As expected, empagliflozin was shown to be a substrate for HEK-293 cells expressing the human SGLT2 transporter. The transport of empagliflozin was found to be saturable and inhibited by phlorizin (PZ) (see sponsor's figure below)

Figure 13. Uptake of Empagliflozin (0.5-1000 uM) by HEK-293 Cells Expressing SGLT2 (sponsor's figure)



The transport of empagliflozin by rat Oatp1a1, Oat3 and mouse oatp1a1, oat3 and human SGLT2 was also time-dependent (see sponsor's figures below).

Figure 14. Time-Dependence of Empagliflozin Transport by Rat Oatp1a1 and Oat3 (sponsor's figure)

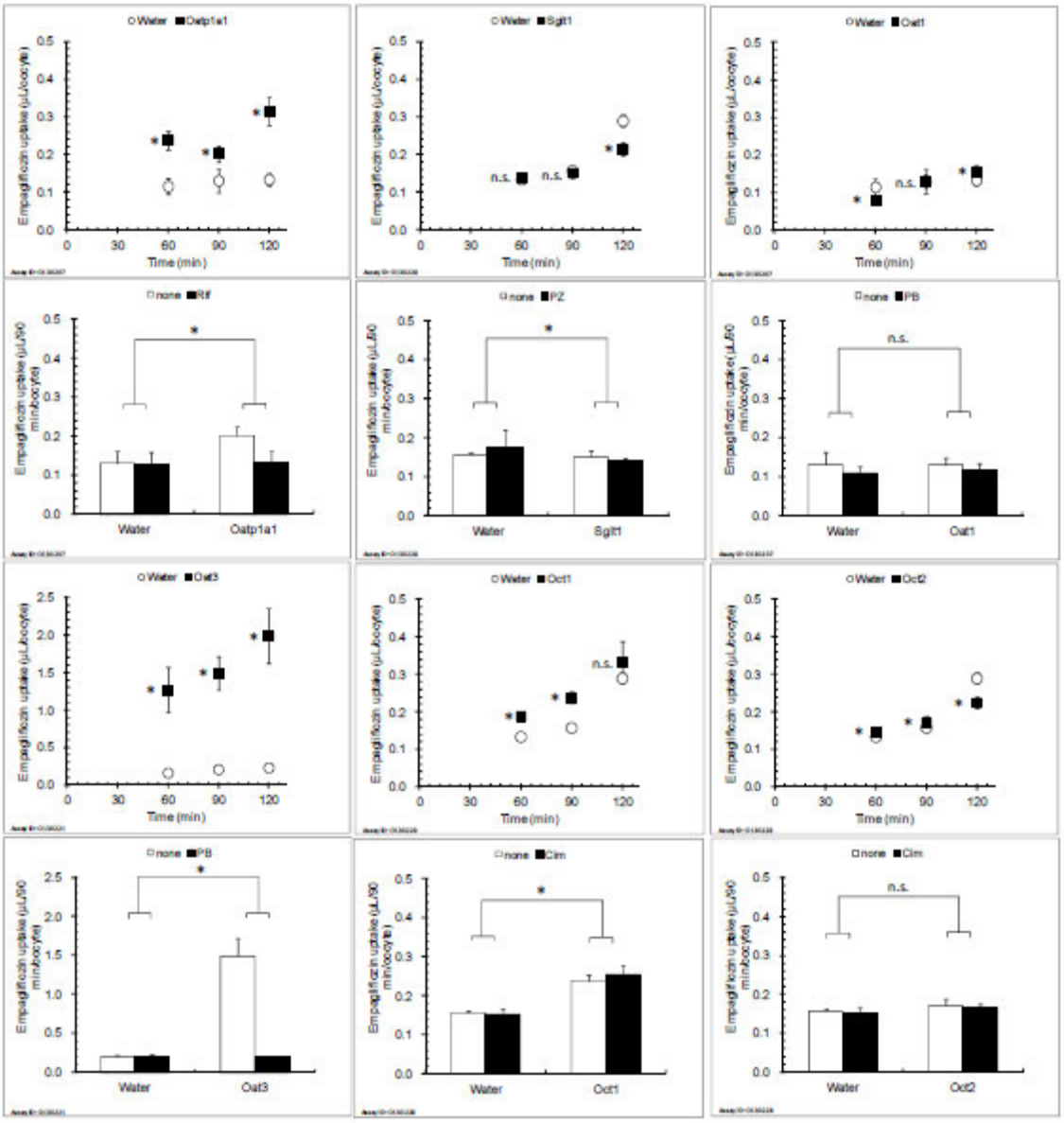


Figure 15. Time-Dependence of Empagliflozin Transport by Mouse oatp1a1and oat3 (sponsor's figure)

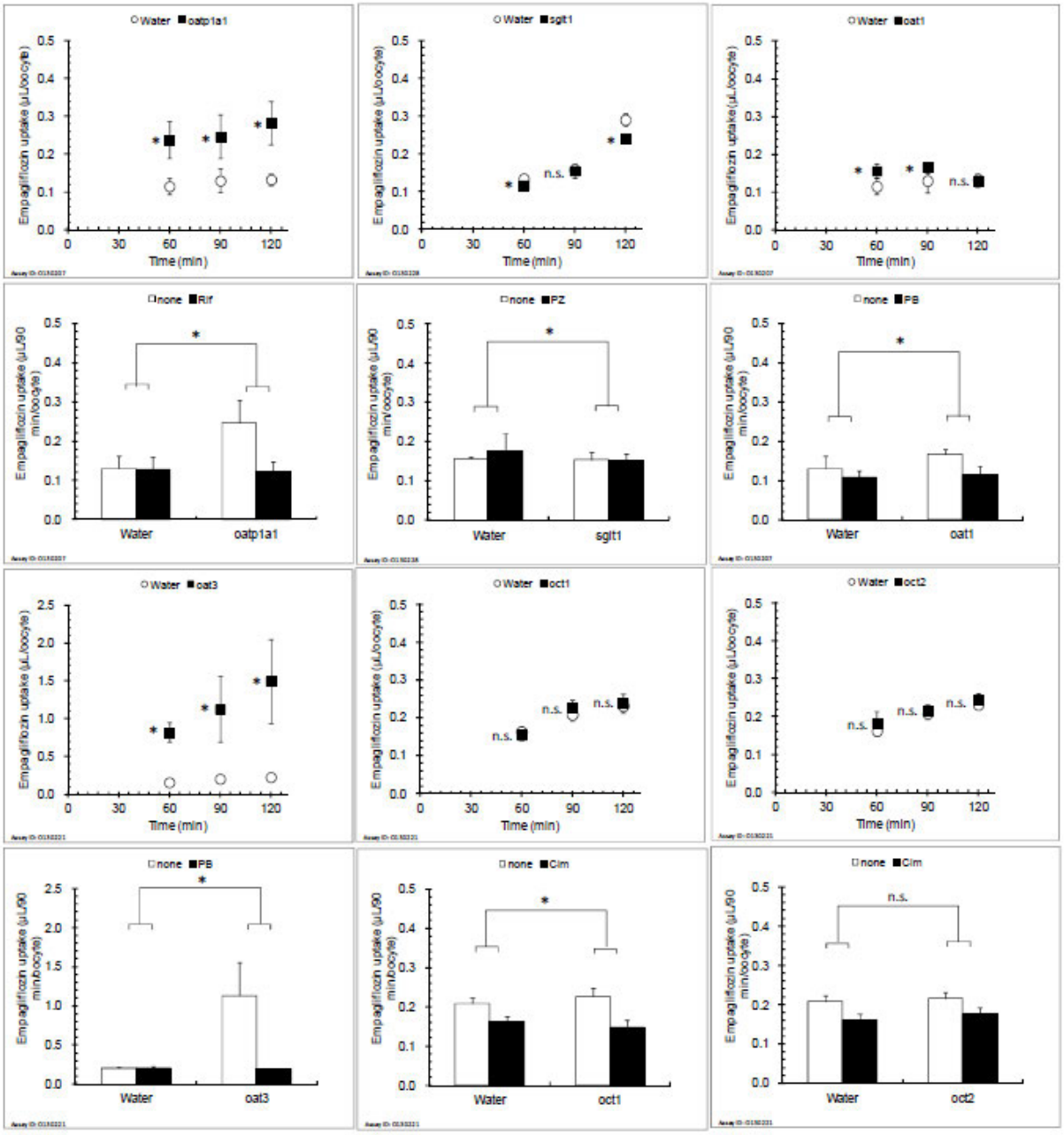
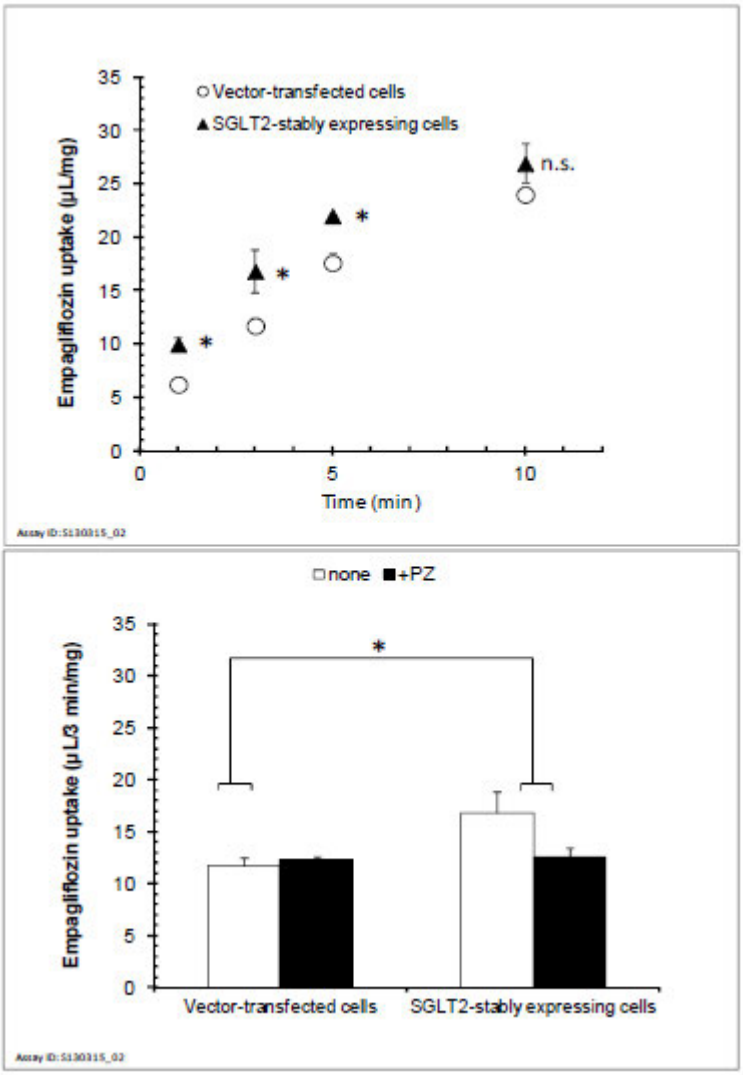


Figure 16. Time-Dependence of Empagliflozin Transport by Human SGLT2 (sponsor's figures)



In Vitro Metabolism

Investigation on the In Vitro Metabolism of [^{14}C]BI 10773 in Mouse, Rat and Human Kidney and Liver (Study# A337-13U, U13-1822-01, non-GLP)

Method

Human (1 male, 2 female), rat (CRl: WI (Han) or mouse (CD-1) liver and kidney microsomes were incubated with [^{14}C]BI 10773 and evaluated for metabolite formation and identification with LC/MS. Additional experiments were conducted in the presence of UDPGA for the identification of glucuronidation metabolites. Further metabolite experiments were conducted using the kidney cytosol of one male and female mouse. NMR was used to identify metabolites. Each tissue subcellular fraction was evaluated for enzyme activity against standard substrates (see sponsor's table below).

Table 11. Species Tissue Fraction Activity Against Standard Substrates (sponsor's table)

Species	Tissue	Sex	Lot	testosterone 6β-hydroxylation [pmol/min/mg protein]	lauric acid 11-hydroxylation	lauric acid 12-hydroxylation	astemizole O-demethylation
Human	Kidney	1m/2f	HKcM280113 p1m2f - Cortex	2.19*	0	735	57.5
Human	Kidney	1m/2f	HKmM280113 p1m2f - Medulla	2.63*	0	252	45.2
Human	Liver	6m/6f	HLM220312p6 m6f	3697	2344	2172	337
Mouse	Kidney	10f	MsKM280113 p10f	39.7	245	1237	10.4
Mouse	Kidney	10 m	MsKM280113 p10m	166	2576	4856	10.7
Mouse	Liver	10f	MsLM310113 p10f	2660	2328	387	24.8
Mouse	Liver	10 m	MsLM310113 p10m	1959	2777	2144	42.5
Rat	Kidney	2f	RWHKM220113p2f	4.40*	2164	5513	12.2
Rat	Kidney	3m	RWHKM220113p3m	4.62*	1651	3987	11.6
Rat	Liver	2f	RWHLM290113p2f	2170	1415	149	136
Rat	Liver	3m	RWHLM290113p3m	2900	2500	1088	149

*: BLR

BLR= below linear range

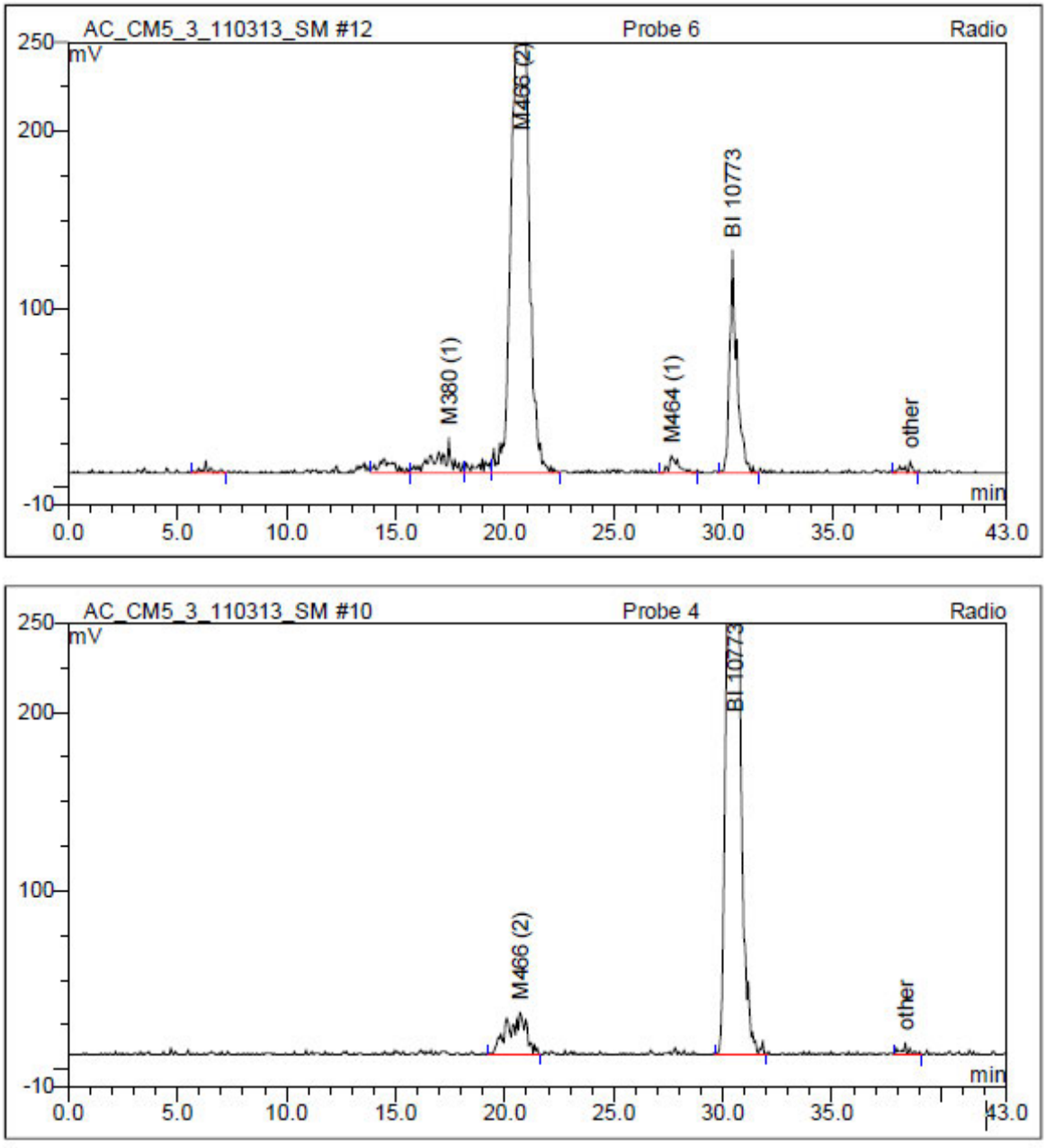
Results

Mouse Kidney

Incubation of male mouse kidney microsomes (0.5 mg protein/mL) with [^{14}C]BI 10773 at 8.9 uM resulted in extensive metabolism of empagliflozin and the formation of metabolite M466(2) as the major metabolite and M380(1) and M464(1) as minor metabolites. Incubation of female mouse kidney microsomes (0.25 mg protein/mL) with

[^{14}C]BI 10773 at 8.9 uM resulted in little metabolism of empagliflozin, but the formation of metabolite M466(2) as a metabolite with no other metabolites formed, suggesting little metabolism had occurred with the female kidney microsomes (see sponsor's figure below).

Figure 17. Incubation of Mouse# Kidney Microsomes With [^{14}C]BI 10773 (sponsor's figure)



#Male kidney microsomes – top panel; Female kidney microsomes – bottom panel

The formation of M466(2) was shown to be linear with respect to time and kidney protein concentration in both the male and female mouse kidney microsomes. (sponsor's male mouse figures and tables are shown below as an example of the sponsor's data).

Figure 18. Male Mouse Kidney Microsomal Metabolite M466(2) Formation Over Time (sponsor's figure)

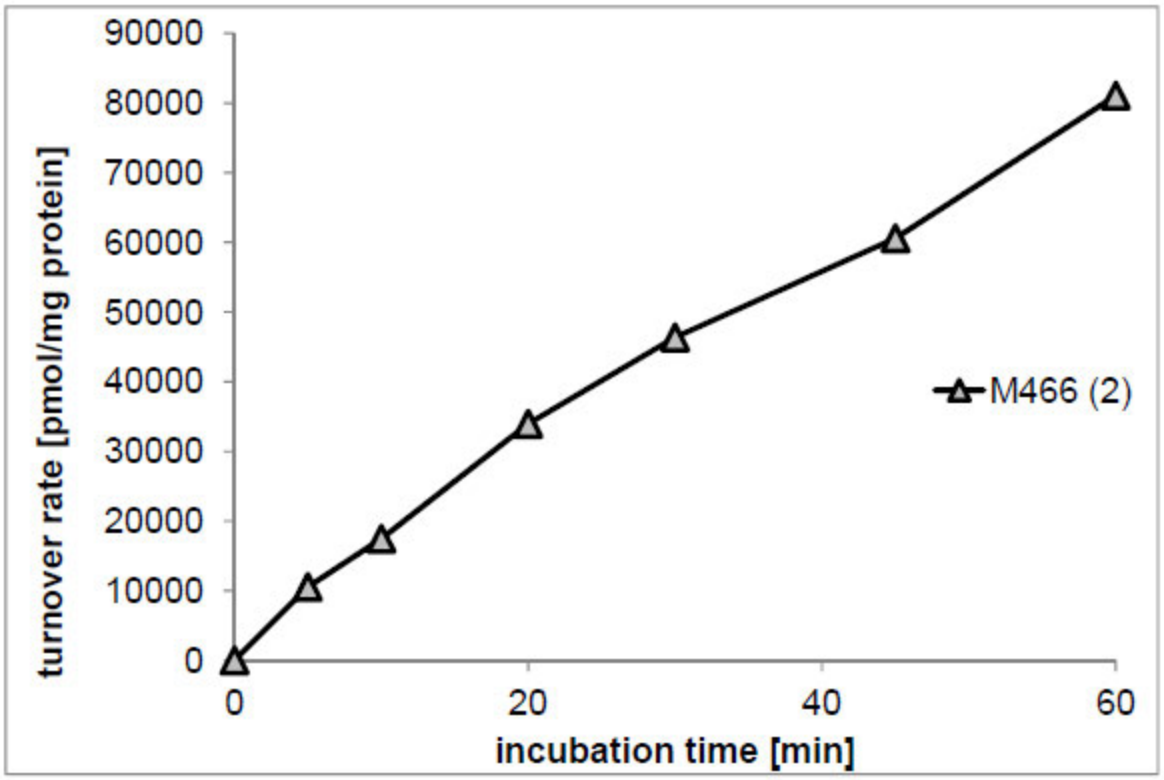
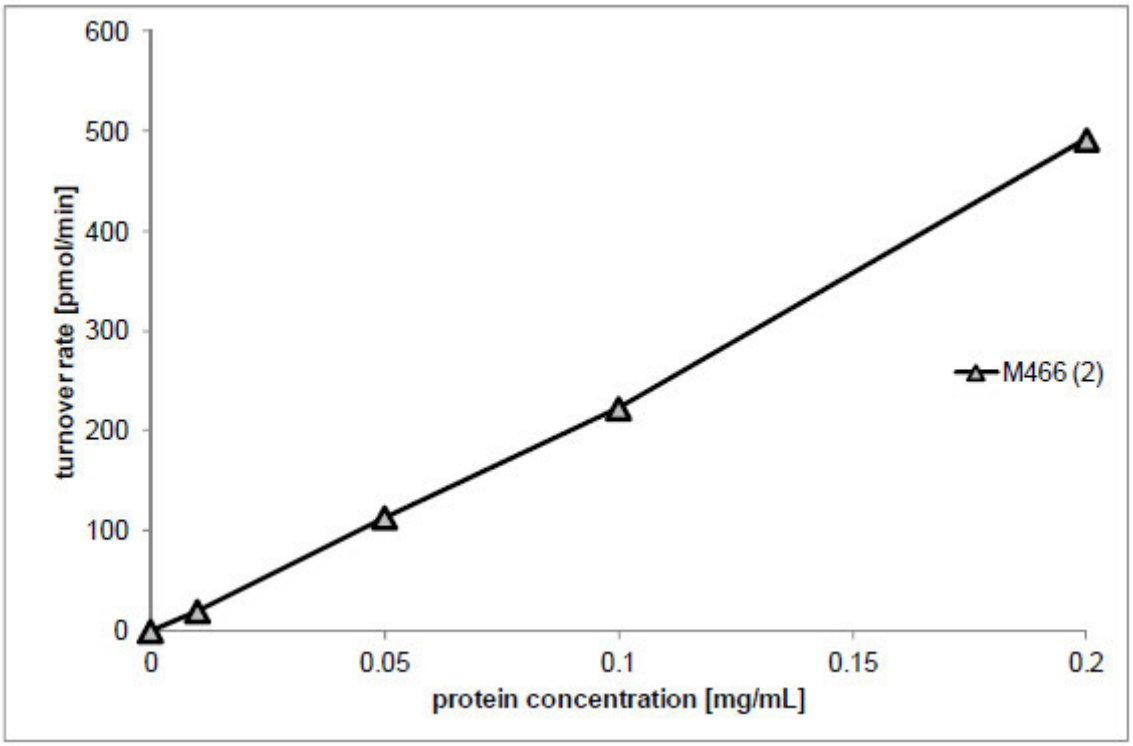


Figure 19. Male Mouse Kidney Microsomal Metabolite M466(2) Protein Concentration Dependence (sponsor's figure)



As can be seen in the (sponsor's) tables below M466(2) was the major metabolite and M380(1) a minor metabolite in male mouse kidney microsomes (0.05 mg protein/mL). M466(2) was the only metabolite in in female mouse kidney microsomes (0.25 mg protein/mL) (see sponsor's table below).

Table 12. Male Mouse Kidney Microsomal Metabolite Formation With BI 10773 (sponsor's table)

Incubation time [min]	mean % of total peak areas						
	M482 (1)	M468 (1)	M380 (1)	M466 (2)	M464 (1)	BI 10773	other
0	NOP	NOP	NOP	NOP	NOP	99.58	0.43
5	NOP	NOP	NOP	5.55	NOP	93.96	0.49
10	NOP	NOP	NOP	9.19	NOP	89.96	0.85
20	NOP	NOP	NOP	17.88	NOP	81.21	0.93
30	NOP	NOP	0.52	24.41	NOP	75.08	NOP
45	NOP	NOP	1.87	31.90	NOP	65.82	0.42
60	NOP	NOP	2.40	42.67	NOP	54.43	0.50
60 [a]	NOP	NOP	NOP	NOP	NOP	99.15	0.86

a: control without NADPH

NOP = no peak found

Table 13. Female Mouse Kidney Microsomal Metabolite Formation With BI 10773
NOP = no peak found (sponsor's table)

Incubation time [min]	mean % of total peak areas corrected for control					
	M482 (1)	M468 (1)	M380 (1)	M466 (2)	M464 (1)	other
0	0	0	0	0	0	0
5	0	0	0	1.26	0	0
10	0	0	0	2.34	0	0
20	0	0	0	4.03	0	0
30	0	0	0	5.86	0	0
45	0	0	0	7.46	0	0
60	0	0	0	9.48	0	0

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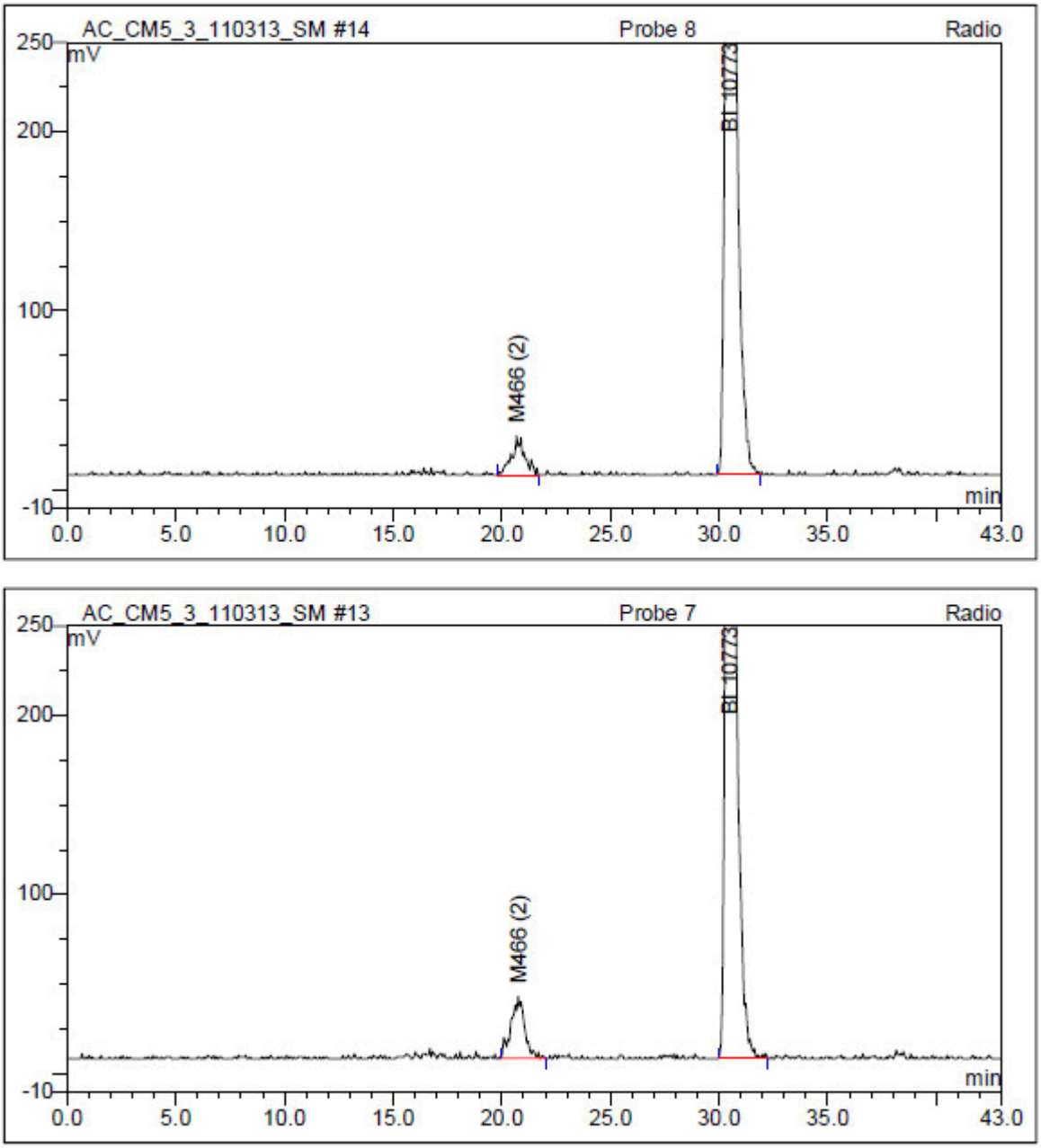
Mouse Liver

Incubation of male and female mouse liver microsomes (0.5 mg protein/mL) with [^{14}C]BI 10773 at 10 μM (10 minute incubation) resulted in the formation of low amounts of metabolite M466(2) as the only metabolite in both genders (see sponsor's figure below).

Figure 20. Incubation of Mouse# Liver Microsomes With [^{14}C]BI 10773 (sponsor's figure)



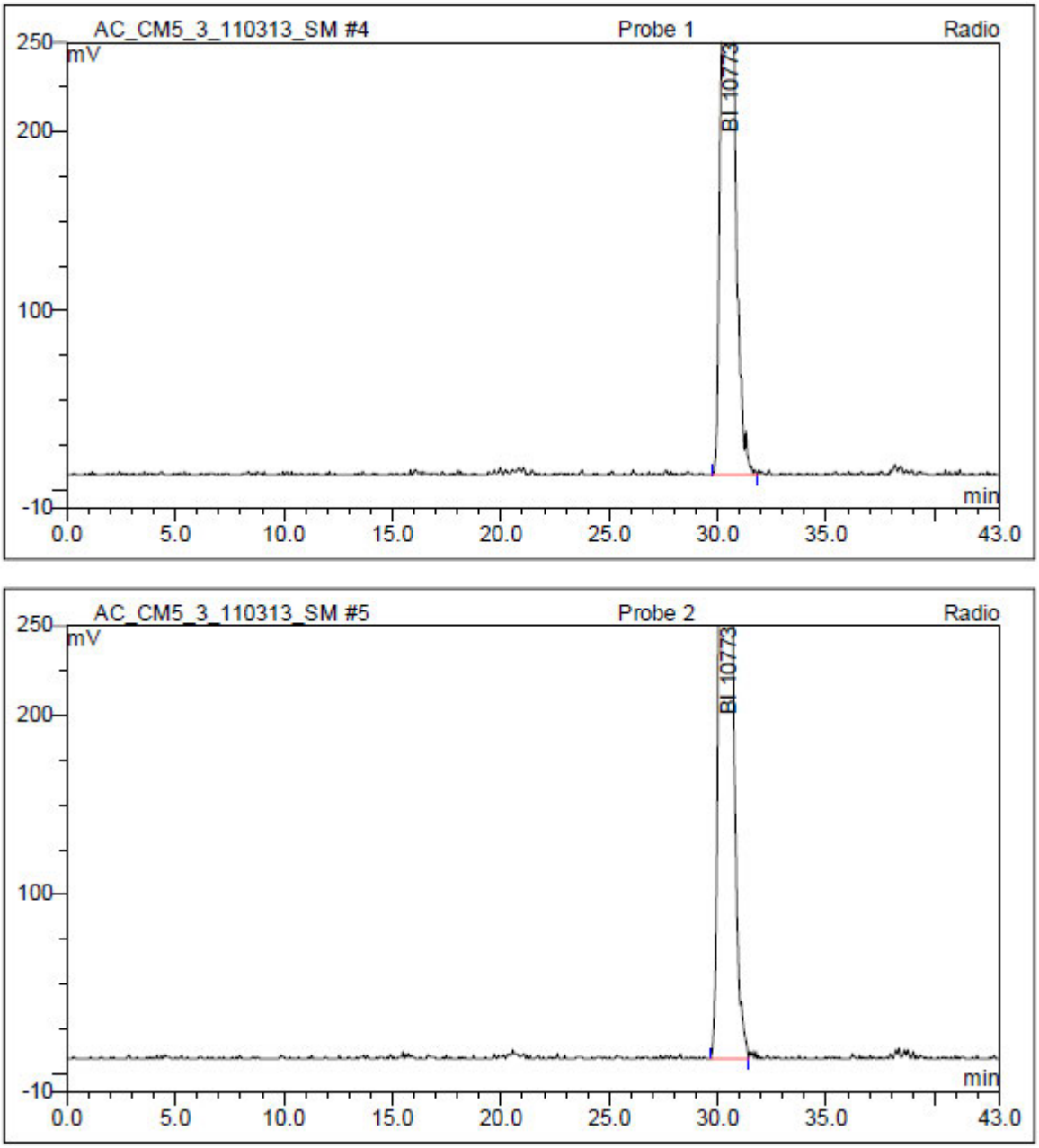
#Male liver microsomes – top panel; Female liver microsomes – bottom panel

As for the kidney microsomes above, the formation of M466(2) was shown to be linear with respect to time and liver protein concentration in both the male and female liver microsomes (results not shown).

Human Kidney and Liver

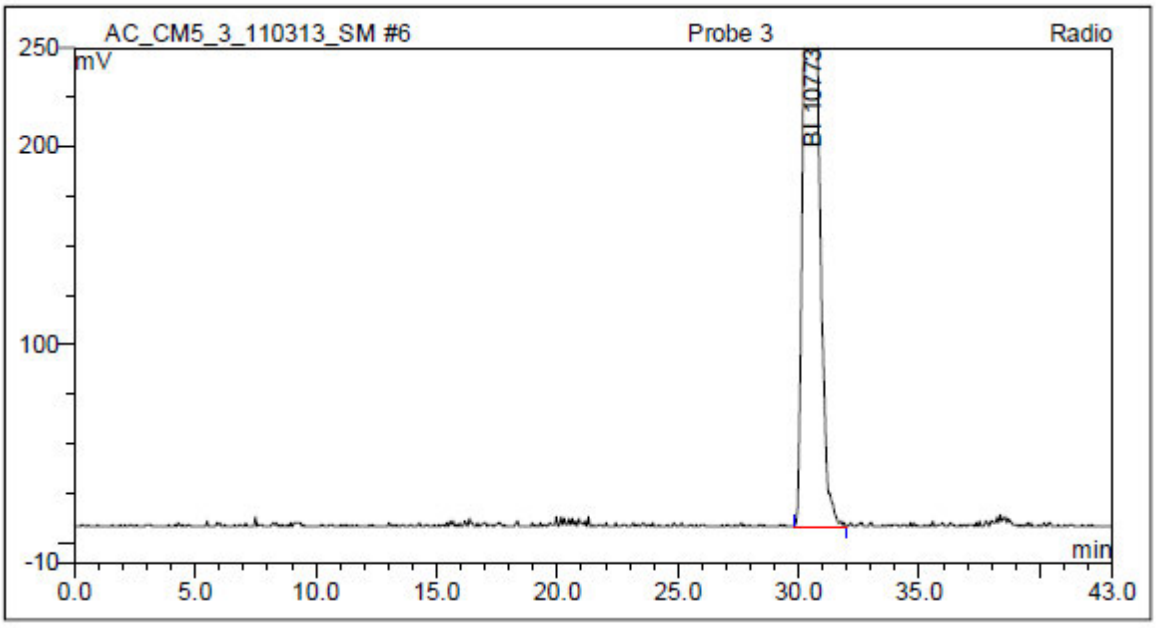
Incubation of microsomes from the human kidney cortex, kidney medulla or liver (0.5 mg protein/mL) with [^{14}C]BI 10773 at 9.3 μM for 10 minutes did not result in metabolite formation (see sponsor's figures below). **Reviewer note: The human male (n=2) and female (n=1) liver or kidney tissues, respectively, were combined prior to tissue homogenization.**

Figure 21. Incubation of Human Kidney# Microsomes With [^{14}C]BI 10773 (sponsor's figure)



#Human kidney cortex microsomes – top panel; Human kidney medulla microsomes – bottom panel

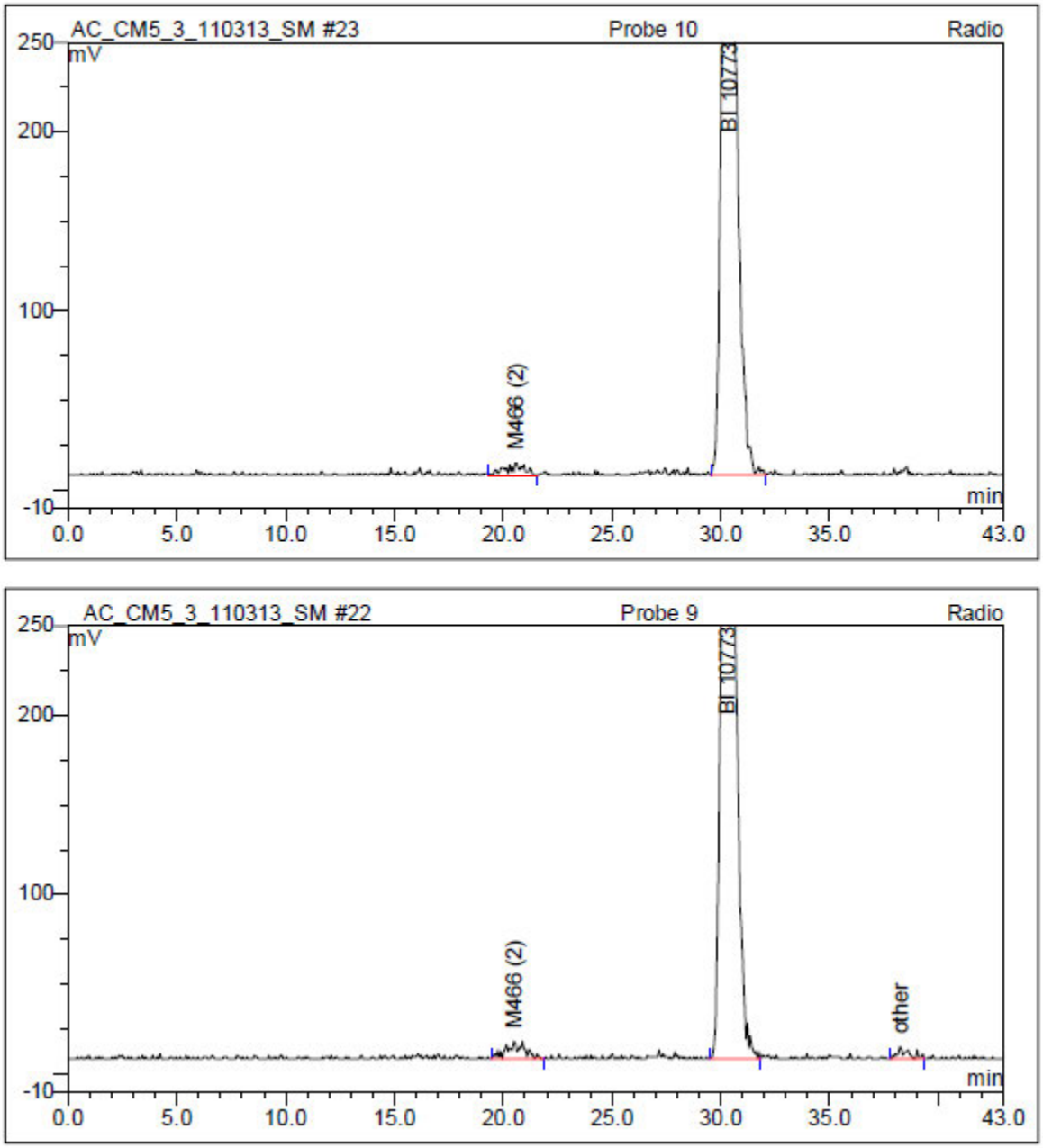
Figure 22. Incubation of Human Liver Microsomes With [^{14}C]BI 10773 (sponsor's figure)



Rat Kidney Microsomes

Incubation of male and female rat kidney microsomes (0.5 mg protein/mL) with [^{14}C]BI 10773 at 10 μM for 10 minutes, resulted in the formation of low amounts (males <2% and females 2.5% of total peak areas) of metabolite M466(2). M466(2) was the only metabolite identified (see sponsor's figure below).

Figure 23. Incubation of Rat Kidney# Microsomes With [^{14}C]BI 10773 (sponsor's figure)

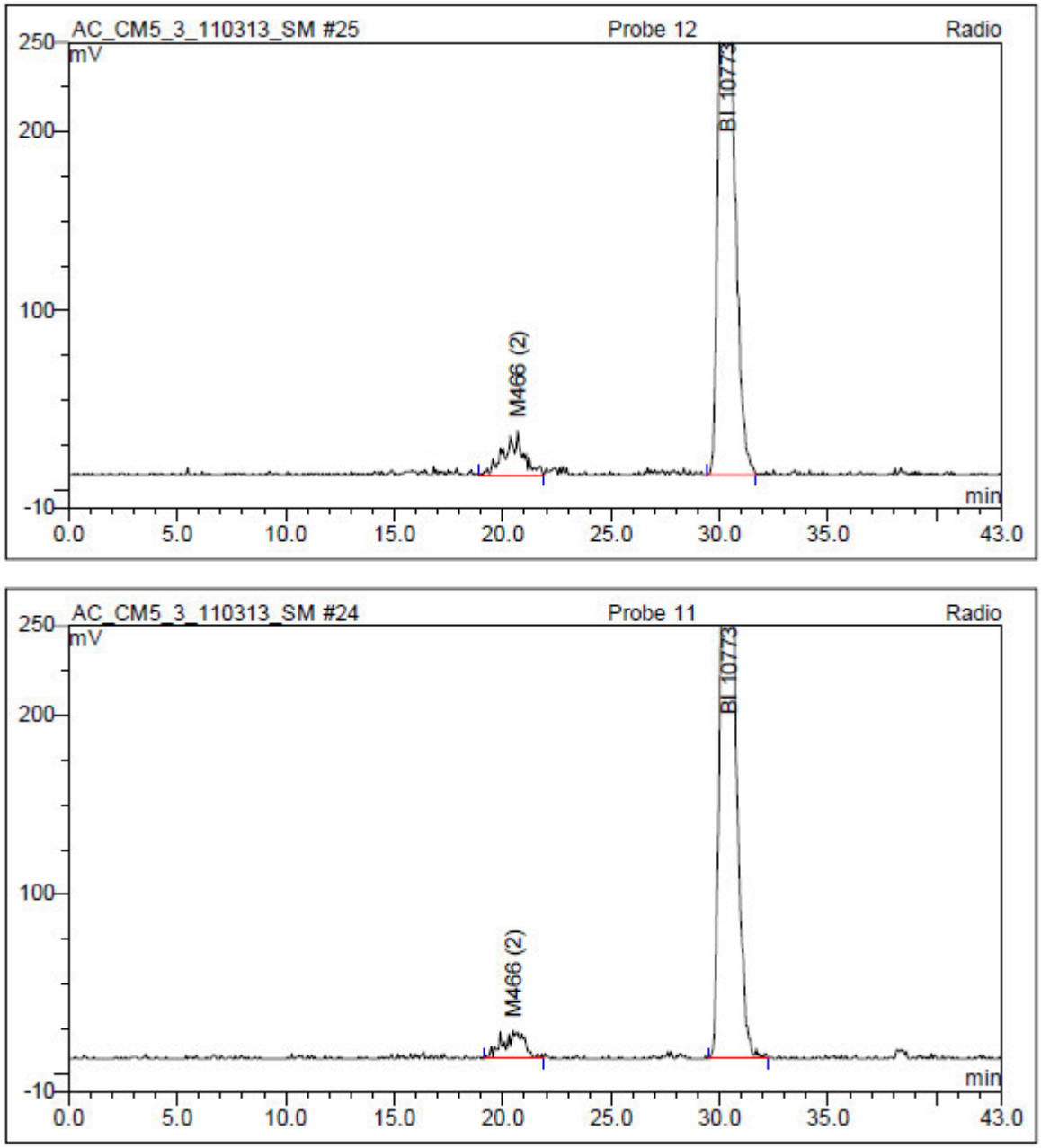


#Male – top panel; Female – bottom panel

Rat Liver Microsomes

Incubation of male and female rat liver microsomes with [^{14}C]BI 10773 at 10 μM for 10 minutes, resulted in the formation of low amounts (approx. 7% of total peak areas) of metabolite M466(2). M466(2) was the only metabolite identified (see sponsor's figure below).

Figure 24. Incubation of Rat# Liver Microsomes With [^{14}C]BI 10773 (sponsor's figure)



#Male – top panel; Female – bottom panel

Species Comparison

With a sponsor-defined optimal protein concentration and incubation time, human liver and kidney, mouse liver, rat liver and kidney microsomes (0.5 mg/mL, 10 min and [^{14}C]BI 10773 at 9.1 uM), male mouse kidney microsomes (0.05 mg/mL, 20 min [^{14}C]BI 10773 at 9.5 uM) and female mouse kidney microsomes (0.25 mg/mL, 30 min and [^{14}C]BI 10773 at 9.4 uM), respectively, were incubated with [^{14}C]BI 10773. Male mouse

kidney microsomes produced the largest amount of M466(2) (see sponsor's figure and table below).

Reviewer note: This is an expected outcome, as it is well established in the literature that male mouse kidney microsomes have a greater P450 activity compared to the female kidney microsomes.

Figure 25. Species Comparison of Metabolite Formation With BI10773 (sponsor's figure)

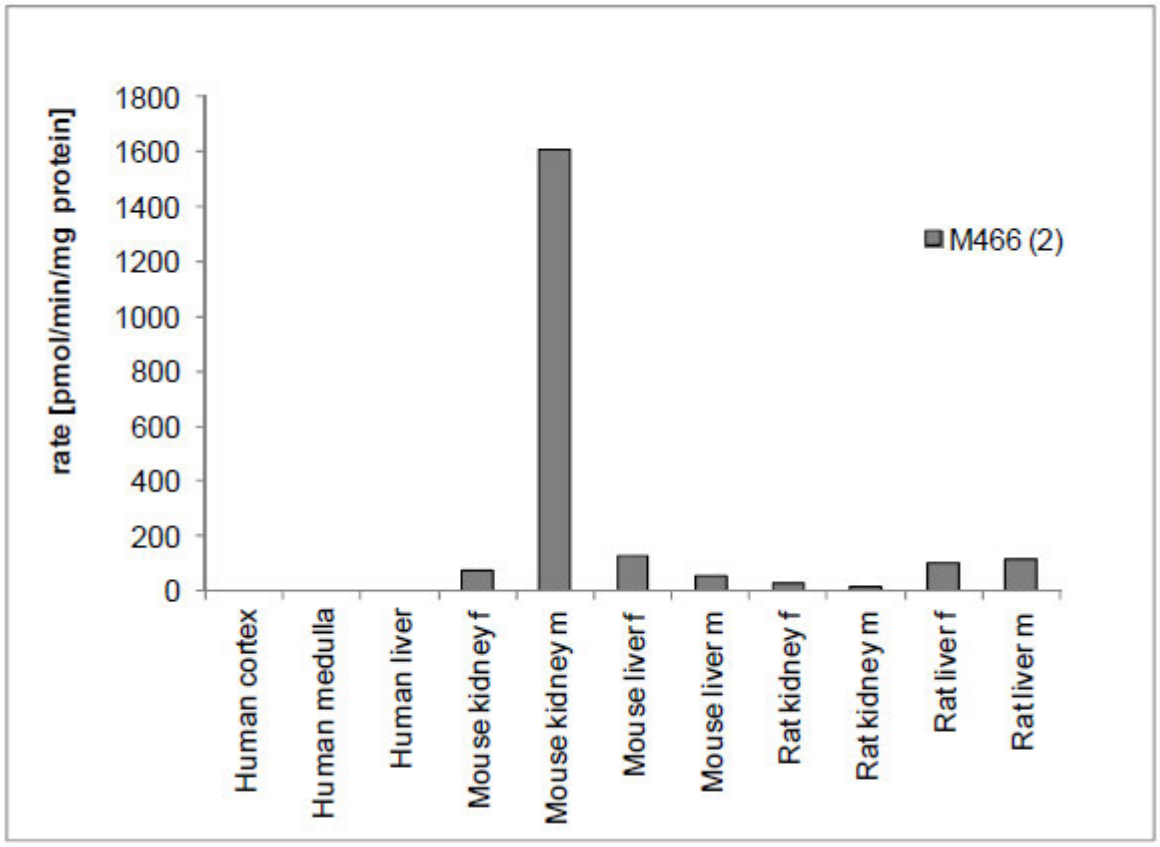


Table 14. Species Comparison of Metabolite Formation With BI10773 (sponsor's table)

tissue	BI 10773 [µM]	protein [mg/mL]	time [min]	mean % of total peak areas M482 (1)	M468 (1)	M380 (1)	M466 (2)	M464 (1)	BI 10773	other
Human cortex	9.3	0.5	10	NOP	NOP	NOP	NOP	NOP	100.00	NOP
Human medulla	9.1	0.5	10	NOP	NOP	NOP	0.85	NOP	98.69	0.47
Human liver	9.1	0.5	10	NOP	NOP	NOP	BLR	NOP	99.52	NOP
Mouse kidney f	9.4	0.25	30	NOP	NOP	NOP	6.79	NOP	93.21	NOP
Mouse kidney m	9.5	0.05	20	NOP	NOP	NOP	17.88	NOP	81.21	0.93
Mouse liver f	9.1	0.5	10	NOP	NOP	NOP	7.92	NOP	91.39	0.40
Mouse liver m	9.1	0.5	10	NOP	NOP	NOP	4.06	NOP	94.93	1.02
Rat kidney f	9.1	0.5	10	NOP	NOP	NOP	2.51	NOP	97.00	0.49
Rat kidney m	9.1	0.5	10	NOP	NOP	NOP	1.78	NOP	97.76	0.47
Rat liver f	9.1	0.5	10	NOP	NOP	NOP	6.47	NOP	93.06	0.48
Rat liver m	9.1	0.5	10	NOP	NOP	NOP	7.13	NOP	92.38	NOP

Per the sponsor's table above (and % of total peak areas), male mouse kidney microsomes produced metabolite M466/2 at 3-fold higher than female mouse kidney microsomes and 2-4-fold higher than mouse liver microsomes, 7-10-fold higher than rat kidney microsomes, 2-3-fold higher than rat liver microsomes and 21-fold higher than human kidney (medulla) microsomes.

Mouse Kidney Tissue Fractions

Mouse kidney microsomes, cytosol or S9 supernatant, respectively (0.2 or 0.5 mg protein/mL), were incubated with 10 μM BI 10773 from 5-15 minutes. Incubation of BI 10773 with female mouse kidney S9 or kidney cytosol produced low amounts of M466(2) (0.65-0.88% total peak areas) as the only metabolite. Incubation of BI 10773 with female mouse kidney microsomes also produced low amounts of M466(2) (1.81-2.01% total peak areas)(see sponsor's table below).

Incubation of BI 10773 with male kidney S9 produced M466(2) as the major metabolite (approx.10-12% of total peak areas), followed by M468 (approx. 6-8% of total peak areas) and a low amount of M380 (approx. 1% of total peak areas). Incubation of male kidney microsomes with BI 10773 produced a 2-fold increase in M466(2) (approx. 24% of total peak areas) when compared to male kidney S9; and a low amount of M380 (approx. 1% of total peak areas).

Figure 26. Mouse Kidney Tissue Fractions (sponsor's figure)

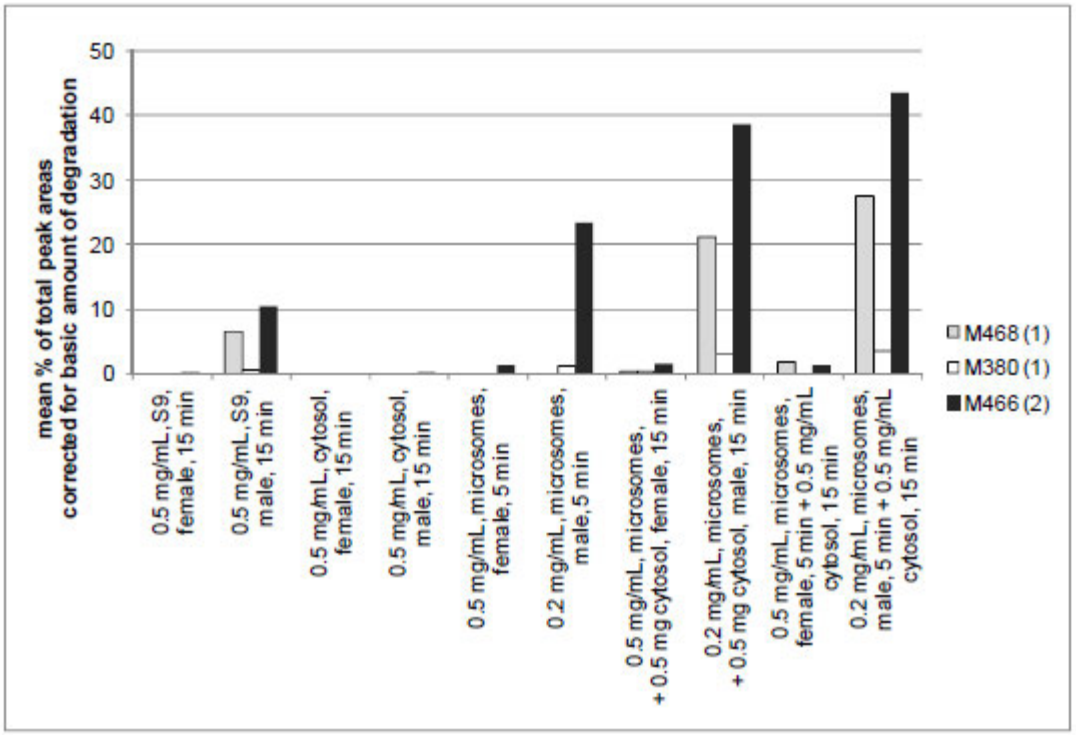


Table 15. Mouse Kidney Tissue Fractions (sponsor's table)

matrix	sex	time [min]	protein [mg/mL]	mean % of total peak areas corrected for basic amount of degradation products M482 (1)	M468 (1)	M380 (1)	M466 (2)	M464 (1)	other
S9	female	15	0.5	0	0	0	0.13	0	BLR
S9	male	15	0.5	0	6.58	0.58	10.42	0	BLR
cytosol	female	15	0.5	0	0	0	0	0	BLR
cytosol	male	15	0.5	0	0	0	0.14	0	0.85
microsomes	female	5	0.5	0	0	0	1.24	0	0.94
microsomes	male	5	0.2	0	0	1.27	23.33	0	0.76
microsomes + cytosol	female	15	0.5 + 0.5	0	0.43	0.35	1.44	0	0.85
microsomes + cytosol	male	15	0.2 + 0.5	0	21.23	3.07	38.76	0.86	0.38
microsomes + cytosol #	female	5 + 15	0.5 + 0.5	0	1.8	0	1.36	0	0.35
microsomes + cytosol #	male	5 + 15	0.2 + 0.5	0	27.64	3.47	43.61	1.24	0

#) preincubation of microsomes and substrate for 5 min, addition of cytosol and additional incubation for 15 min

Species Comparison of BI 10773 Glucuronide Formation

Human kidney cortex, medulla or human liver (1 mg protein/mL) were incubated with 9.5 uM [^{14}C]BI 10773 for 30 minutes. The glucuronide metabolite (M626(1)) of empagliflozin was formed in low amounts in the human kidney cortex and medulla and also the human liver (see sponsor's table below). Low amount of M626(1) were also formed by the mouse liver but not the male or female mouse kidney (see sponsor's table below).

Table 16. Glucuronide Formation of BI 10773 in Various Species Tissue Fractions (sponsor's table)

tissue	% of total peak areas M482 (1)	M380 (1)	M468 (1)	U8	M464 (1)	M466 (2)	M626 (1) #	BI 10773
parent	NOP	NOP	NOP	NOP	NOP	NOP	NOP	100.00
Human cortex	NOP	NOP	NOP	0.72	NOP	NOP	2.31	96.97
Human cortex	NOP	NOP	NOP	0.68	NOP	NOP	2.43	96.89
Human medulla	NOP	NOP	NOP	0.91	NOP	NOP	1.57	97.52
Human medulla	NOP	NOP	NOP	NOP	NOP	NOP	1.44	98.56
Human liver	NOP	NOP	NOP	0.73	NOP	NOP	1.14	98.13
Human liver	NOP	BLR	NOP	0.97	NOP	NOP	1.02	97.49
Mouse kidney f	NOP	0.61	NOP	NOP	NOP	NOP	NOP	99.39
Mouse kidney f	NOP	NOP	NOP	NOP	NOP	NOP	NOP	100.00
Mouse kidney m	NOP	NOP	NOP	0.83	NOP	NOP	NOP	99.17
Mouse kidney m	NOP	NOP	NOP	0.72	NOP	NOP	NOP	99.28
Mouse liver f	NOP	NOP	NOP	0.70	NOP	NOP	0.68	98.62
Mouse liver f	NOP	NOP	NOP	NOP	NOP	NOP	BLR	99.37
Mouse liver m	NOP	NOP	NOP	1.19	NOP	NOP	1.21	97.60
Mouse liver m	NOP	NOP	NOP	1.03	NOP	NOP	1.15	97.82
without enzyme	NOP	NOP	NOP	0.83	NOP	NOP	NOP	98.56
without enzyme	NOP	NOP	NOP	0.65	NOP	NOP	NOP	98.80

#: M626(1) = BI 10773 glucuronide

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Bioanalysis of M466/2 (BI00737687) and M380/1, and Identification of the 4-hydroxycrotonaldehyde-GSH adduct from the degradation of M466/2 in Phosphate Buffer in the Presence of Glutathione (Study# DM-13-1129, U13-3897-01, non-GLP)

Method

Empagliflozin metabolite M466/2 (100 uM or 300 uM) was incubated with 0.04% [^{3}H]-GSH/99.96% GSH at 37°C for 0.2, 4, 6, 14, 16, 18, 20, 22, 24 or 40 hr (in duplicate). A similar incubation with M466/2 was conducted under the same conditions with unlabeled GSH. At each time point the reaction was quenched and a 100 uL aliquot removed for analysis. Metabolites were identified using LC/MS/MS and a radiomatic detector. Authentic standards of M466/2 and M380/1 were used to confirm degradation/formation of metabolites and produce standard curves.

Results

Incubation of empagliflozin metabolite M466/2 in the presence or absence of glutathione (GSH) (labeled/unlabeled) resulted in the formation of metabolite M380/1 as identified by LC/MS/MS. The formation of metabolite M380/1 appeared to occur at the same rate over the 24 hr incubation period regardless of the presence/absence of GSH (see sponsor's tables below for incubations of M466/2 at 100 or 300 uM). The formation of M380/1 (and degradation of parent M466/2) is in general linear up to 18 hr and then plateaus in both incubations.

Table 17. Metabolite M380/1 Formation from 100 uM M466/2 in the Presence of GSH (sponsor's table)

Time (h)	[M466/2], µM	[M380/1], µM	[M466/2] + [M380/1], µM	% of M466/2 remaining, %	% of M380 formed, %
0	68.2	0[1]	68.2[2]	100	N/A
2	64.1	33.5	97.6	65.7	34.3
4	45.3	52.1	97.4	46.5	53.5
6	32.7	62.9	95.6	34.2	65.8
8.25	23.8	75.6	99.4	23.9	76.1
16	10.5	95.3	106	9.88	90.1
18	9.05	109	118	7.69	92.3
20	6.86	96.6	103	6.63	93.4
22	5.91	110	116	5.09	94.9
24	4.64	110	115	4.04	96.0

[1] M380/1 concentration in 10X diluted samples at 0 hour was below the lower limit of quantitation (0.313 uM).
[2] The measured concentration of M466/2 at 0h was only 68% of the nominal concentration.

Table 18. Metabolite M380/1 Formation from 100 uM M466/2 in the Absence of GSH (sponsor's table)

Time[1] (h)	[M466/2], µM	[M380/1], µM	[M466/2] + [M380/1], µM	% of M466/2 remaining, %	% of M380 formed, %
0	59.4	0[2]	59.4[3]	100	N/A
2	66.8	24.7	91.5	73.0	27.0
4	65.6	47.5	113	58.0	42.0
6	43.4	54.0	97.3	44.6	55.4
8.25	33.0	64.5	97.4	33.8	66.2
16	16.8	97.9	115	14.6	85.4
18	14.4	115	129	11.1	88.9
20	11.7	111	122	9.57	90.4
24	7.52	123	130	5.78	94.2

[1] M380/1 concentration at 22h was higher than those at 20h and 24h. It was considered as an outlier and not reported.
[2] M380/1 concentration in 10X diluted samples at 0 hour was below the lower limit of quantitation (0.313 uM).
[3] The measured concentration of M466/2 at 0h was only 59% of the nominal concentration.

Table 19. Metabolite M380/1 Formation from 300 uM M466/2 in the Presence of GSH (sponsor's table)

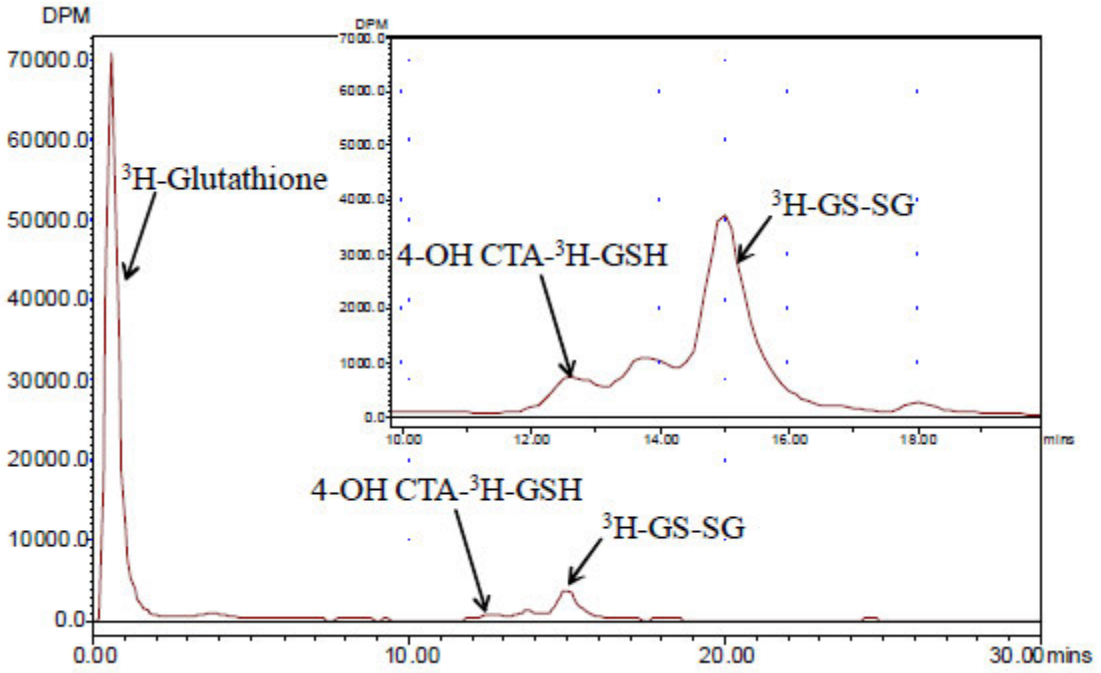
Time (h)	[M466/2], µM	[M380/1], µM	[M466/2] + [M380/1], µM	% of M466/2 remaining, %	% of M380 formed, %
0	275	8.21	283	97.1	2.90
2	203	91.2	294	69.0	31.0
4	179	165	344	52.0	48.0
6	114	197	310	36.6	63.4
8.25	89.7	258	348	25.8	74.2
16	30.2	302	332	9.10	90.9
18	24.8	329	353	7.01	93.0
20	20.6	300	321	6.43	93.6
22	14.9	322	337	4.41	95.6
24	14.6	330	345	4.24	95.8

Table 20. Metabolite M380/1 Formation from 300 uM M466/2 in the Absence of GSH (sponsor's table)

Time (h)	[M466/2], µM	[M380/1], µM	[M466/2] + [M380/1], µM	% of M466/2 remaining, %	% of M380 formed, %
0	266	6.25	272	97.7	2.30
2	235	69.0	304	77.3	22.7
4	211	134	344	61.2	38.8
6	167	185	352	47.5	52.5
8.25	121	226	347	34.9	65.1
16	48.7	299	347	14.0	86.0
18	47.5	324	372	12.8	87.2
20	30.9	308	338	9.12	90.9
22	25.3	328	353	7.15	92.9
24	24.2	332	356	6.78	93.2

Incubation of M466/2 at 300 uM with [^{3}H]-GSH resulted in limited formation of a 4-hydroxycrotonaldehyde (4-OH-CTA)-glutathione (-[^{3}H-GSH] adduct as a minor metabolite (identified in a radiochromatogram) (see sponsor's figure below). Oxidized glutathione (^{3}H-GS-SG) was the next major component with much of the GSH being unchanged (see sponsor's figure below). Identical results (not shown) were obtained with M466/2 at 100 uM.

Figure 27. Representative Chromatogram of M466/2 incubated with [3H]-GSH for 24 hr (sponsor's figure)



For the incubation of M466/2 at 300 uM with [^{3}H]-GSH from 14-40 hours the estimated concentration of 4-OH-CTA-[^{3}H-GSH] adduct was 52.5 uM or 17.5% (see sponsor's table below)

Table 21. Estimated 4-hydroxycrotonaldehyde (4-OH-CTA)-glutathione (-[^{3}H-GSH] adduct Formation from 300 uM M466/2 (sponsor's table)

Time (h)[1]	M466/2 (300 µM)[1,2]	
	Radioactivity of 4-OH CTA-[^{3}H]-GSH (dpm)	Estimated [4-OH CTA-GSH] (µM)
14	4929.4	42.8
16	6065.0	52.6
18	7603.8	66.0
20	7712.4	66.9
22	5262.2	45.7
24	5804.2	50.4
40	4955.2	43.0
Mean [4-OH CTA-GSH] from 14 to 40h (µM)[3]	52.5	

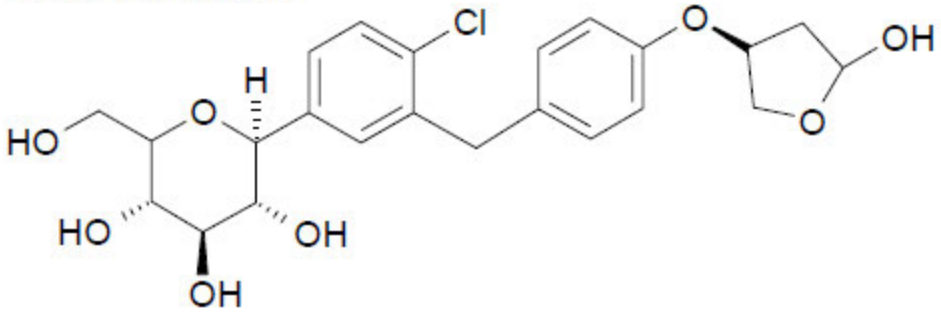
[1]Radioactivity of 4-OH CTA-[^{3}H]-GSH in time points before 14 h (0, 2, 4 and 6h) was not detected.
[2]The radioactivity signals in samples from the 100 µM incubation were low and the concentrations of 4-OH CTA-GSH adduct were not calculated at 100 µM of M466/2.
[3]The concentrations of 4-OH CTA-GSH adduct were similar between time points from 14h to 40h. Therefore, the mean concentration of 4-OH CTA-GSH was calculated by averaging the concentrations at 14, 16, 18, 20, 22, 24 and 40h.

MS-MS was used to confirm the identity of the 4-OH-CTA-[^{3}H-GSH] adduct (data not shown). The structures, formula and weights of M466/2, M380/1 and 4-OH-CTA are shown below (sponsor's figures).

Figure 28. Structures, Formula and Weights of M466/2, M380/1 and 4-hydroxycrotonaldehyde (4-OH-CTA) (sponsor's figures)

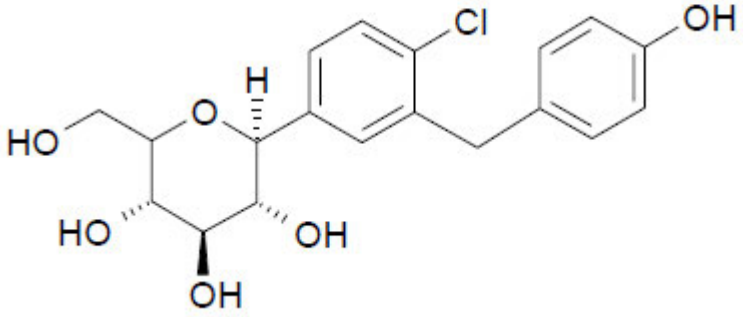
M466/2 (BI 00737687)

Test Substance:	M466/2 (BI00737687)
Lot Number:	102950-038
Empirical Formula:	$C_{23}H_{27}ClO_8$
Formula Weight:	466 g/mole
Chemical Structure:	



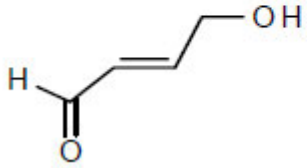
M380/1

Analyte:	M380/1
Empirical Formula:	$C_{19}H_{21}ClO_6$
Formula Weight:	380.83 g/mole
Chemical Structure:	



4-OH -CTA

Analyte:	4-hydroxycrotonaldehyde
Empirical Formula:	$C_4H_6O_2$
Formula Weight:	86.09 g/mole
Chemical Structure:	



Overall, under the conditions of the assay the unstable degradation product of the empagliflozin, metabolite M466/2, was found to degrade to M380/1, but also to an unstable 4-OH-CTA that was trapped with glutathione to form a 4-OH-CTA-GSH adduct.

In Vitro Studies With Empagliflozin (BI 10773) in Mouse Primary Renal Tubular Epithelial Cells (Study# 13R083, U13-3468-01, non-GLP)

Method

Primary mouse renal tubular epithelial cells were isolated and pooled from the cortex of 6-7 week old CD-1 mice. Following culture for 7-8 days, these cells were treated with BI 10773 at 0.1-100 μM or 300 μM. The sponsor used this range to cover the approx. human plasma exposure (1 μM) and the approx. C_{max} in the 2 year mouse carcinogenicity study (100 μM). Cell proliferation was assessed by BrdU-incorporation ELISA and cytotoxicity was assessed with a luminescent ATP-cell viability assay. Fetal bovine serum (FBS) (10%) and recombinant human epidermal growth factor (rhEGF) were used as the positive controls in the BrDU-assay. The insecticide rotenone or the antimicrobial valinomycin were used as the positive controls for the cytotoxicity assay

Results

Mouse renal tubular epithelial cell proliferation via BrDU incorporation was assessed 16-20 hours post-BI 10773 (empagliflozin) treatment. BI 10773 had no effect on cell proliferation. FBS and rhEGF increased cell proliferation as expected and produced an approx. 2-fold increase in BrDU incorporation (see sponsor's table below). Cell counting confirmed the lack of BrDU-incorporation (data not shown).

Treatment of male mouse renal tubular epithelial cells with empagliflozin at 0-100 uM did not result in ATP depletion as a measure of cell cytotoxicity (see sponsor's table below). Rotenone and valinomycin were used as positive control treatments which resulted in 0.8-54% depletion of ATP.

Table 22. BrDU-Incorporation in Male Mouse Renal Tubular Epithelial Cells Following Treatment with Empagliflozin at 0-100 uM (sponsor's table)

Experiment	Units	BI 10773 (µM) 100.0	30.0	10.0	3.0	1.0	0.3	0.1	Positive Control EGF	10% FBS	DMSO vehicle	No treatment
1	OD_{370}	0.29	0.28	0.25	0.26	0.31	0.26	0.26	0.61	0.51	0.24	0.38
	% of DMSO	121.9	118.5	108.3	108.9	130.4	111.9	109.6	260.2	214.9	100.0	161.7
2	OD_{370}	0.22	0.28	0.28	0.25	0.25	0.23	0.25	0.52	0.51	0.20	0.25
	% of DMSO	111.1	141.7	139.7	126.6	123.1	115.0	124.0	259.4	253.9	100.0	126.3
3	OD_{370}	0.14	0.14	0.16	0.16	0.15	0.15	0.15	0.26	0.41	0.14	0.11
	% of DMSO	97.0	99.5	111.6	109.3	102.3	106.7	106.0	183.1	284.8	100.0	76.2
Mean % of DMSO		110.0	119.9	119.9	114.9	118.6	111.2	113.2	234.2	251.2	100.0	121.4
Std. Dev. % of DMSO		12.5	21.1	17.3	10.1	14.6	4.2	9.5	44.3	35.0	0.0	43.0

Table 23. ATP Depletion in Male Mouse Renal Tubular Epithelial Cells Following Treatment with Empagliflozin at 0-100 uM (sponsor's table)

Experiment	Units	BI 10773 (µM) 300.0	100.0	30.0	10.0	3.0	1.0	0.3	0.1	Positive Control	DMSO vehicle	No treatment
1	RLU	93679.1	84887.2	84457.3	84470.7	97420.9	88743.6	81338.1	79630.2	41198.0*	76456.8	
	% of DMSO	122.5	111.0	110.5	110.5	127.4	116.1	106.4	104.2	53.9*	100.0	
2	RLU		170036.8	162686.9	167597.2	162631.9	155883.7	155034.4	159893.2	21779.0	153402.39	190623.0
	% of DMSO		110.8	106.1	109.3	106.0	101.6	101.1	104.2	14.2	100.0	124.3
3	RLU	108450.5	108869.0	106122.9	106192.1	107536.6	107783.5	109411.7	108396.3	789.6	94740.4	107780.0
	% of DMSO	114.5	114.9	112.0	112.1	113.5	113.8	115.5	114.4	0.8	100.0	113.8
Mean % of DMSO		118.5#	112.3	109.5	110.6	115.6	110.5	107.6	107.6		100.0	119.0#
Std. Dev. % of DMSO		#	2.3	3.1	1.4	10.9	7.8	7.3	5.9		0.0	#

Values are from n= 2 experiments. All others from n=3 experiments.
* Positive control values are from rotenone. All other positive control values are from valinomycin.

Overall, in vitro treatment with empagliflozin in mouse renal tubular cells did not result in cell cytotoxicity or cell proliferation. Thus, when evaluated in vitro, empagliflozin is not directly cytotoxic or mitogenic to mouse renal tubular epithelial cells.

In Vivo Metabolism

BI 10773 XX Metabolite Profiling and Tentative Metabolite Identification in CD-1 Mouse Kidney (Study# DM-13-1002, U13-3477-02, non-GLP)

Method

Male and female CD-1 mice (n=8/sex) were treated with a single oral administration of 1000 mg/kg [^{14}C] BI 10773. Mouse kidneys were harvested at 1 and 4 hours post-dose and pooled according to gender and time point. Metabolites were identified by LC/MS/MS and radiochromatography.

Results

Empagliflozin (BI 10773) was the most abundant component of the female mouse kidney at 1 hr and 4 hr post-dose, representing 70.9% (1 hr) and 45.8% (4 hr) of the total radioactivity (see sponsor's table below). Metabolite M482/1 was the most abundant metabolite representing 12.1% and 30% of the radioactivity at 1 and 4 hr post-dose, respectively. This was followed by metabolites M464/1, M468/1 and M380/1 at

less than 10% of the total radioactivity (see sponsor's metabolites below). Other metabolites in the female kidney were at less than 1% of the total radioactivity.

Similarly, in the male kidney, empagliflozin (BI 10773) was the most abundant component at 1 hr and 4 hr post-dose, representing 29.2% (1 hr) and 25.5% (4 hr) of the total radioactivity (see sponsor's table below).
Metabolite M482/1 was the most abundant metabolite representing 19.6% and 25.5% of the radioactivity at 1 and 4 hr post-dose, respectively. This was followed by metabolites M468/1 (20.7% at 1 hr and 21.7% at 4 h post-dose), M464/1 (15.9% at 1 hr and 13.1% at 4 hr) and M380/1 at less than 10% of the total radioactivity (see sponsor's metabolites below). Other metabolites in the male kidney were at less than 2.5%% of the total radioactivity.

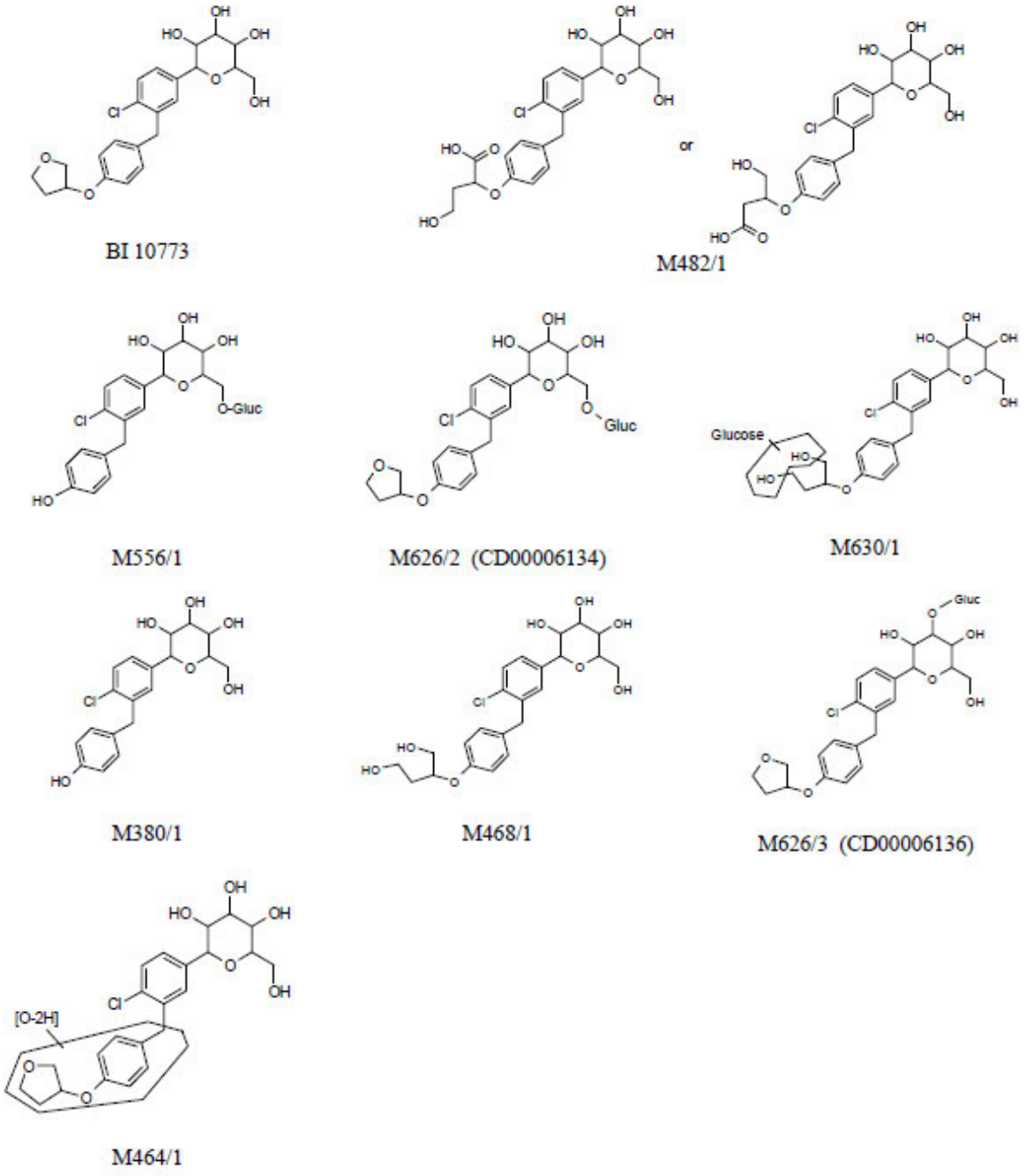
Table 24. Metabolites of BI 10773 Following a Single Oral 1000 mg/kg Administration (sponsor's table)

Radioactivity contributions of BI 10773 and metabolites in mouse kidney										
Metabolites	Male 1h		Male 4h		Female 1h		Female 4h		Male/Female (conc.)	
	% [^{14}C] [a]	nM [d]	% [^{14}C]	nM	% [^{14}C]	nM	% [^{14}C]	nM	1 h	4 h
Total ^{14}C	100	650000	100	418000	100	585000	100	204000	1.2	1.2
M556/1	0.9	5590	0.5	1880	0.8	4860	0.7	1510	1.2	1.2
M482/1	19.6	127000	24.9	104000	12.1	70800	30.0	61100	1.8	1.7
M626/2	1.2	7480	ND [b]	ND	ND	ND	ND	ND	NA [c]	NA
M630/1	1.3	8450	2.5	10300	ND	ND	0.4	876	NA	11.7
M380/1	7.9	51600	8.8	36600	2.7	15700	6.3	12800	3.3	2.9
M468/1	20.7	134000	21.7	90600	4.1	23700	6.5	13300	5.7	6.8
M626/3	1.5	9490	2.2	8990	ND	ND	1.0	2120	NA	4.2
M464/1	15.9	103000	13.1	54900	5.1	29800	7.1	14400	3.5	3.8
BI 10773	29.2	190000	25.5	107000	70.9	415000	45.8	93200	0.5	1.1

[a] % of sample radioactivity[1]
[b] Not detected
[c] Not applicable
[d] nM is based on nmole/kg-tissue

Metabolites M482/1, M468/1, M464/1 and M380/1 are primarily oxidative metabolites (see sponsor's figure below). Of note, at the 1 and 4 hr time points abundant oxidative metabolites such as M482/1, M380/1 and M468/1 were found to be 1.8-1.7-fold, 3.3-2.9-fold and 5.7-6.8-fold more abundant, respectively, in males than females, thus showing a gender bias in metabolite formation.

Figure 29. Structure of BI 10773 Metabolites in the CD-1 Mouse Kidney Following a Single Oral Administration of 1000 mg/kg (sponsor's figure)



6 General Toxicology

6.2 Repeat-Dose Toxicity

A 7 Day Renal Function and Toxicity Study With BI 10773 in CD-1 Mice

Study no.:	U13-3465-01 (12r144)
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 10th 2012
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	BI 10773, 15 and

Key Study Findings

Methods

(b) (4)

Reviewer note: In addition to clinical chemistry and urinalysis, renal function was determined by examination of gene expression profiling in one- and seven-day treated male and female mice. Histopathology specimens were collected but not analyzed.

Observations and Results

Mortality/Clinical Signs

No mortality was observed. No "overt" clinical signs manifested.

Body Weights

At 24 hours post-dose, mean body weight (BW) was dose-dependently reduced 4% and 7% in the 100 and 1000 mg/kg males; and 3% and 5% in the 100 and 1000 mg/kg females, respectively (see sponsor's table below). At study termination (day 8) mean BW was dose-dependently reduced 5% and 11% in the 100 and 1000 mg/kg males; and 2% and <1% in the 100 and 1000 mg/kg females, respectively (see sponsor's table below). **Reviewer note: statistical significance was not assessed; however, reduced BW is a known pharmacodynamic response of SGLT2 inhibition, so these results are not unexpected.**

Table 25. BW at Day 2 (24-hr Treated Mice) (sponsor's table)

Male Mean Body Weights (g) for Group:

Day		0 mg/kg	100 mg/kg	1000 mg/kg
-1	Mean:	33.0	32.8	33.2
	SD	0.88	0.85	1.09
2	Mean:	29.8	28.7	27.6
	SD	1.81	0.67	1.15

Female Mean Body Weights (g) for Group:

Day		0 mg/kg	100 mg/kg	1000 mg/kg
-1	Mean:	25.3	25.7	25.8
	SD	1.22	0.81	0.80
2	Mean:	22.5	23.2	21.4
	SD	0.88	0.75	0.96

Table 26. BW at day 8 (7-day Treated Mice) (sponsor's table)

Male Mean Body Weights (g) for Group:

Day		0 mg/kg	100 mg/kg	1000 mg/kg
-1	Mean:	32.9	33.0	32.6
	SD	1.04	1.12	0.93
8	Mean	32.1	30.5	28.7
	SD	1.54	1.14	2.29

Female Mean Body Weights (g) for Group:

Day		0 mg/kg	100 mg/kg	1000 mg/kg
-1	Mean:	25.9	25.5	25.4
	SD	1.00	1.39	1.29
8	Mean:	23.8	23.3	23.9
	SD	1.49	1.45	1.22

Feed Consumption/Ophthalmoscopy/ECG/Hematology

Not assessed.

Clinical Chemistry

BUN was increased 16% and 43% above control in the 100 and 1000 mg/kg males, respectively at day 8. BUN was also increased 39% in the 1000 mg/kg females on day 8. **Reviewer note: this is likely due to increased protein catabolism as a consequence of caloric loss due to glucosuria, which is a known pharmacodynamic consequence of SGLT2 inhibition.**

Table 27. Clinical Chemistry (sponsor's table)

			BUN (mg/dL)		Enz Cr (mg/dL)		Total Bilirubin (mg/dL)	
			Day 2	Day 8	Day 2	Day 8	Day 2	Day 8
1M	0 mg/kg	Mean	28.60	21.38	0.09	0.09	0.11	0.14
		SD	6.21986	3.04332	0.01317	0.02309	0.02514	0.02079
2M	100 mg/kg	Mean	26.18	24.89*	0.09	0.09	0.10	0.13
		SD	4.79254	4.14741	0.01524	0.01337	0.01229	0.02150
3M	1000 mg/kg	Mean	27.38	30.60*	0.08	0.09	0.10	0.11
		SD	3.59098	5.64427	0.01494	0.01059	0.01853	0.02675
1F	0 mg/kg	Mean	23.06	19.56	0.10	0.10	0.09	0.13
		SD	3.66551	3.15743	0.00632	0.01265	0.00843	0.03706
2F	100 mg/kg	Mean	21.66	20.81	0.10	0.10	0.09	0.12
		SD	4.85894	4.07252	0.01703	0.01434	0.00632	0.02452
3F	1000 mg/kg	Mean	24.99	27.10*	0.10	0.09	0.10	0.10
		SD	4.11459	5.20427	0.01449	0.01265	0.02234	0.01160

*P< 0.05

Urinalysis

Urine volumes were significantly increased approx. 2-fold in the 100 and 1000 mg/kg females at day 2. Urine volume was also significantly increased 2-fold in the 1000 mg/kg females at day 8. Urine volume was also increased 1- and 2-fold in the 100 and 1000 mg/kg males at day 8, respectively (see sponsor's table below)

Urinary glucose was dose-dependently significantly increased 463- and 502-fold in the 100 and 10000 mg/kg males, respectively at day 2. Urinary glucose was dose-dependently significantly increased 263- and 303-fold in the 100 and 10000 mg/kg females, respectively at day 2. Similarly at day 8, urinary glucose was dose-dependently significantly increased 813-, 849-fold (males), 223- and 264-fold (females) in the 100 and 10000 mg/kg males and females respectively, (see sponsor's table below).

Table 28. Urinalysis (sponsor's table)

			Volume (mL)		Osmolality (mOsm/kg)		Na (mmol/L)	
			Day 2	Day 8	Day 2	Day 8	Day 2	Day 8
1M	0 mg/kg	Mean	1.803	2.5	1252.778	1013.3	78.778	59.800
		SD	1.452691	1.027402	247.5453	238.5279	19.32471	11.50652
2M	100 mg/kg	Mean	1.85	3.5*	1846.1*	1573.9*	69.200	54.500
		SD	0.579751	0.666667	343.9743	209.3129	17.19690	7.97566
3M	1000 mg/kg	Mean	1.675	4.35*	2056.22*	1604.8*	86.889	30.500*
		SD	0.646035	0.914391	227.2327	226.2156	9.66236	19.36348
1F	0 mg/kg	Mean	0.777778	1.675	1392	1363.11	104.286	62.222
		SD	0.551198	0.83375	288.7622	361.9632	48.50331	17.39093
2F	100 mg/kg	Mean	1.4*	2.2	2104.5*	1784.9*	77.400	49.500
		SD	0.459468	0.483046	204.1776	307.8006	18.53046	9.69822
3F	1000 mg/kg	Mean	1.4*	4.15*	2235.8*	1651.1*	84.000*	28.900
		SD	0.614636	1.355032	278.5086	141.4877	17.43560	10.57723

*P< 0.05

Table 28. Urinalysis (sponsor's table) continued

			Glu (mg/dL)		Ca (mg/dL)		Phos (mg/dL)	
			Day 2	Day 8	Day 2	Day 8	Day 2	Day 8
1M	0 mg/kg	Mean	24.66667	13.78	7.011111	6.71	308.3222	308.41
		SD	8.766271	10.16539	1.898318	3.812975	125.061	95.14126
2M	100 mg/kg	Mean	11432.8*	11212.6*	3.27*	4.4	266.48	242*
		SD	1375.914	1890.367	0.987758	1.400793	95.60591	57.47881
3M	1000 mg/kg	Mean	12397.78*	11692.55*	5*	8.83	301.9444	230.34*
		SD	1719.337	2195.529	1.834394	6.570312	60.09946	30.23865
1F	0 mg/kg	Mean	46.35714	48.04444	11.0625	10.77	527.425	495.83
		SD	18.99411	51.83558	3.004253	3.885886	224.9287	197.805
2F	100 mg/kg	Mean	12183.15*	10694.55*	7.32	7.22	397.14	360.62
		SD	1953.423	2019.464	0.971597	3.401242	92.00931	85.38156
3F	1000 mg/kg	Mean	14070.65*	12691.3*	8.04	9.27	337.83	281.15*
		SD	1914.613	1684.289	2.561336	5.807093	53.63409	65.00112

*P< 0.05

When assessed as a function of mean 24 hr excretion, urinary glucose was significantly and dose-dependently increased in both the BI10773-treated males (452-490-fold) and females (391-449-fold) at day 2. At day 8, the mean urinary glucose excretion was further (significantly and dose-dependently) increased 320-733-fold in the 100 and 1000 mg/kg females and 1135- and 1510-fold in the 100 and 1000 mg/kg males, respectively (see sponsor's table below).

Table 29. Urinalysis - 24 Hour Excretion (sponsor's table)

			Na (umol)		K (umol)		Cl (umol)	
			Day 2	Day 8	Day 2	Day 8	Day 2	Day 8
1M	0 mg/kg	Mean	138.83	143.60	314.58	350.33	124.33	127.40
		SD	49.289	51.958	190.009	143.434	56.038	52.604
2M	100 mg/kg	Mean	123.40	187.95*	250.01	439.28	94.90	148.75
		SD	32.614	30.474	76.246	114.542	24.047	37.931
3M	1000 mg/kg	Mean	157.89	133.85	257.75	551.65*	105.11	163.30
		SD	35.873	79.004	43.455	120.296	27.980	56.778
1F	0 mg/kg	Mean	82.43	109.17	171.21	340.36	86.14	126.78
		SD	24.125	41.248	80.557	105.049	29.915	40.385
2F	100 mg/kg	Mean	103.25	108.05	243.00	346.48	103.45	113.30
		SD	30.097	28.081	93.675	47.631	31.301	30.957
3F	1000 mg/kg	Mean	111.85*	109.25	197.15	589.10*	95.85	148.50
		SD	47.295	37.926	61.408	190.374	39.535	45.282

*P< 0.05

			Glu (mg)		Ca (µg)		Phos (mg)	
			Day 2	Day 8	Day 2	Day 8	Day 2	Day 8
1M	0 mg/kg	Mean	0.46	0.34	139.22	145.00	6.15	7.53
		SD	0.280	0.291	104.522	47.907	5.461	3.614
2M	100 mg/kg	Mean	208.13*	386.05*	58.40*	156.15	4.83	8.56
		SD	60.024	65.449	18.538	66.617	1.902	2.755
3M	1000 mg/kg	Mean	225.53*	513.58*	88.33	349.45*	5.39	9.84
		SD	58.595	147.191	25.521	182.449	0.943	1.585
1F	0 mg/kg	Mean	0.43	0.71	91.31	196.44	3.87	7.83
		SD	0.378	0.579	52.816	121.334	2.239	2.861
2F	100 mg/kg	Mean	168.22*	227.48*	103.50	159.50	5.69	7.65
		SD	58.243	25.733	38.430	91.775	2.352	1.141
3F	1000 mg/kg	Mean	192.94*	520.32*	107.05	398.00	4.53	12.28*
		SD	69.343	176.665	36.455	316.316	1.268	5.164

*P< 0.05

In addition, when assessed as a function of mean 24 hr excretion, urinary sodium (Na), phosphorus (phos) and potassium (K) were increased on either day 2 or 8 (see sponsor's table above). These changes were likely due to osmotic diuresis.

Creatinine clearance was increased 33% and 34% in the 100 and 1000 mg/kg females at day 2 and 38% in the 1000 mg/kg females at day 8 (see sponsor's table below).

Table 30. Mean Creatinine Clearance (sponsor's table)

			CCr (mL/hr/kg) Day 2	Day 8
1M	0 mg/kg	Mean	643.6832	648.5732
		SD	132.5795	256.3496
2M	100 mg/kg	Mean	695.1701	804.7526
		SD	233.3542	184.3219
3M	1000 mg/kg	Mean	808.4885	757.6376
		SD	330.3028	126.0757
1F	0 mg/kg	Mean	442.8366	591.8801
		SD	96.05824	131.4343
2F	100 mg/kg	Mean	590.0463*	633.1904
		SD	115.9835	157.2068
3F	1000 mg/kg	Mean	593.1907*	817.3188*
		SD	128.5047	239.4676

*P< 0.05
Creatinine Clearance was calculated using the following formula
(Urine Volume * Urine Creatinine *1000)/Serum Creatinine*24hr*Body Weight

Urinary Biomarkers

Urinary biomarkers were normalized to creatinine. Urinary Cystatin C was significantly increased 93% and 115% in the 100 and 1000 mg/kg females at day 2. Urinary Cystatin C was significantly increased 149% and 352% in the 100 and 1000 mg/kg females at day 8 (see sponsor's table below). Urinary Cystatin C was not significantly changed in males. This suggests a minimal renal dysfunction as serum cystatin C was unaltered.

Clusterin was significantly increased 2-fold in the 100 and 1000 mg/kg males at day 8. Microalbumin was significantly increased 2- and 4-fold in the 100 and 1000 mg/kg females at day 2. Microalbumin was significantly increased 4-and 6-fold in the 1000 mg/kg males and females, respectively, at day 8. **Reviewer note: clusterin and microalbumin are freely filtered at the glomerulus, reabsorbed but not secreted. The presence of these urinary biomarkers suggests renal tubular injury. However, corroborating histopathology is required to confirm these findings.**

Table 31. Urinary Biomarkers (sponsor's tables)

			Cyst/CR (ng/mg)		mNGAL/CR (ng/mg)		Clusterin/CR (ng/mg)	
			Day 2	Day 8	Day 2	Day 8	Day 2	Day 8
1M	0 mg/kg	Mean	609.17	511.94	211.70	172.76	13.42	11.27
		SD	201.703	144.169	99.550	53.562	9.047	7.216
2M	100 mg/kg	Mean	771.93	813.14	515.56	333.23*	15.55	22.34*
		SD	128.853	192.863	918.912	166.296	8.641	13.233
3M	1000 mg/kg	Mean	668.71	2232.02	289.75	29667.53	10.45	24.54*
		SD	192.917	3485.722	164.762	87651.196	4.729	16.506
1F	0 mg/kg	Mean	204.68	163.46	1502.45	1756.54	5.00	4.82
		SD	209.965	159.220	3710.524	3619.125	8.754	3.568
2F	100 mg/kg	Mean	394.30*	392.68*	504.08	631.31	1.98	3.14
		SD	185.448	211.738	301.311	601.873	0.554	0.652
3F	1000 mg/kg	Mean	440.59*	740.16*	678.73	3052.30	2.37	8.05
		SD	136.264	263.663	613.252	3091.286	0.762	3.663

*P< 0.05

			KIM-1/CR (ng/mg)		Microalbumin/CR(µg/mg)	
			Day 2	Day 8	Day 2	Day 8
1M	0 mg/kg	Mean	3.97	2.95	132.00	124.15
		SD	2.893	2.011	68.087	85.037
2M	100 mg/kg	Mean	2.35	2.25	157.89	171.94
		SD	3.282	1.541	109.805	57.238
3M	1000 mg/kg	Mean	3.30	4.07	181.63	441.38*
		SD	2.184	2.930	81.021	224.716
1F	0 mg/kg	Mean	13.16	3.55	51.84	78.90
		SD	10.630	3.644	41.806	53.700
2F	100 mg/kg	Mean	12.65	9.38	92.35*	134.83
		SD	13.729	8.138	42.941	78.526
3F	1000 mg/kg	Mean	12.37	9.83*	229.28*	448.12*
		SD	15.680	6.391	117.343	266.361

*P< 0.05

Gross Pathology/Organ Weights

Not assessed.

Histopathology

Histopathology specimens of the kidney were collected but not analyzed.

Adequate Battery No

Peer Review No

Histological Findings Not assessed

Special Evaluation

Gene Expression Analysis Using Taqman RT-PCR

The sponsor collected "enriched cortex" kidney tissue from bisected left kidney sections from 5 animals/sex/group. The sponsor elected to analyze a panel of 66 genes related to kidney development and renal function and injury derived from the scientific literature (see Appendix for the tabulated list (sponsor's table). The gene sets comprised genes involved in apoptosis, calcium homeostasis, cell cycle proliferation, chemokines, ER stress, cell adhesion and fibrosis, hypoxia signaling, early injury response, lipid metabolism, NO signaling, oxidative stress and transport activity. Gene expression significance was set at ≥2-fold and $p<0.05$.

Of the 66 kidney target genes differentially expressed in the male relative to vehicle groups included 5 up regulated genes and 2 down regulated genes (see sponsor's table below). Similarly, only 4 differentially expressed genes were observed in the BI 10773-treated females (see sponsor's table below). None of these genes appear to be relevant to the pharmacology effects of empagliflozin.

Table 32. Differentially Expressed Genes in BI 10773-Treated Males (sponsor's table)

	Day 2				Day 8			
	100 mg/kg		1000 mg/kg		100 mg/kg		1000 mg/kg	
Gene Symbol	Fold change	*p* value	Fold change	*p* value	Fold change	*p* value	Fold change	*p* value
Trpv6	1.73	0.172	**2.50**	**0.000**	1.08	0.420	1.16	0.225
Myc	1.44	0.413	**2.20**	**0.018**	0.91	0.632	**2.60**	**0.020**
Slc22a12	1.49	0.085	**2.01**	**0.002**	1.04	0.727	1.01	0.959
Rac1	1.47	0.172	**2.00**	**0.000**	1.00	0.989	1.00	0.967
Mt1	1.16	0.402	1.53	0.000	1.43	0.002	**2.07**	**0.012**
Fos	1.38	0.447	0.77	0.472	0.75	0.380	**0.45**	**0.042**
Slco1a1	1.05	0.954	0.63	0.421	**0.19**	**0.044**	0.61	0.274

*Bold indicates over 2 fold changes in expression with statistical significance ($p<0.05$). Source data: Appendix Table 3.

Table 33. Differentially Expressed Genes in BI 10773-Treated Females (sponsor's table)

	Day 2				Day 8			
	100 mg/kg		1000 mg/kg		100 mg/kg		1000 mg/kg	
Gene	Fold change	*p* value	Fold change	*p* value	Fold change	*p* value	Fold change	*p* value
Slc22a12	0.60	0.0073	0.58	0.0044	0.87	0.3979	**0.48**	**0.0076**
Rac1	**0.49**	**0.0001**	**0.48**	**0.0002**	0.99	0.9214	0.90	0.2247
Fos	**0.49**	**0.0025**	0.84	0.2996	1.00	0.9979	0.76	0.4062
Keap1	**0.42**	**0.0006**	**0.41**	**0.0012**	1.00	0.9872	0.84	0.1395

*Bold indicates over 2 fold changes in expression with statistical significance ($p<0.05$). Source data: Appendix Table 4

When the sponsor conducted a more global gene expression analysis was conducted with the removal of false positives (per the sponsor's own analysis), 33 genes in high dose males (19 up, 14 down) and 15 genes in high dose females (12 up and 3 down) were found with a greater than equal to 2-fold ($p<0.05$) expression change at day 2 (see sponsor's tables below). Upregulated genes include Cyp4a12, Cyp24a1 and aldehyde dehydrogenase 1A7 (Aldh1a7) in both high dose males and females (at day 2).

At day 8, the high dose males and females were found with 17 genes (10 up and 7 down) and 7 genes (3 up and 4 down), respectively, that were found with a greater than equal to 2-fold ($p<0.05$) expression change ($p<0.05$) (see sponsor's tables below). No genes showed similar gene expression in both high dose males and females. In the high dose males the modified genes were unrelated to SGLT2 or metabolism except for Cyp4a14 (see sponsor's table below). In the high dose females the modified genes were unrelated to SGLT2 or metabolism (see sponsor's table).

Table 34. Differentially Expressed Genes Male Day 2 at 1000 mgkg (sponsor's table)

Gene Symbol	Gene Name	Direction	Fold Change	FDR *p* value
Gjb4	gap junction protein, beta 4	Down	299.124	1.151E-03
Gabra3	gamma-aminobutyric acid (GABA) A receptor, subunit alpha 3	Down	22.447	6.430E-03
Ttr	transthyretin	Down	8.078	2.751E-04
Lrrc15	leucine rich repeat containing 15	Down	6.700	4.171E-02
BC021614	cDNA sequence BC021614	Down	6.548	8.019E-03
Hpd	4-hydroxyphenylpyruvic acid dioxygenase	Down	5.790	0.000E+00
Slc14a2	solute carrier family 14 (urea transporter), member 2	Down	4.124	2.006E-02
Cyp24a1	cytochrome P450, family 24, subfamily a, polypeptide 1	Down	3.910	2.035E-07
Slc37a1	solute carrier family 37 (glycerol-3-phosphate transporter), member 1	Down	3.736	3.718E-02
Npas2	neuronal PAS domain protein 2	Down	2.563	3.718E-02
Ptpn22	protein tyrosine phosphatase, non-receptor type 22 (lymphoid)	Down	2.485	1.184E-03
Bok	BCL2-related ovarian killer protein	Down	2.273	3.529E-02
Slc16a14	solute carrier family 16 (monocarboxylic acid transporters), member 14	Down	2.152	3.529E-02
Zfp36	zinc finger protein 36	Down	2.019	3.359E-02
Prss22	protease, serine, 22	Up	98.129	1.134E-07
H2-Ea-ps	histocompatibility 2, class II antigen E alpha, pseudogene	Up	28.610	7.229E-05
Aldh1a7	aldehyde dehydrogenase family 1, subfamily A7	Up	5.498	6.626E-10
Cyp4a14	cytochrome P450, family 4, subfamily a, polypeptide 14	Up	4.773	2.285E-03
Hmgcs2	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2	Up	4.362	1.514E-06
Hspa1a	heat shock protein 1A	Up	4.199	2.852E-07
Hspa1b	heat shock protein 1B	Up	4.177	1.581E-08
Atp4a	ATPase, H+/K+ exchanging, gastric, alpha polypeptide	Up	4.131	5.530E-04
Acot3	acyl-CoA thioesterase 3	Up	3.353	2.895E-07
Gm14403	predicted gene 14403	Up	2.956	2.545E-02
Cyp4a10	cytochrome P450, family 4, subfamily a, polypeptide 10	Up	2.741	2.815E-02
Per2	period circadian clock 2	Up	2.412	5.803E-03
Manf	mesencephalic astrocyte-derived neurotrophic factor	Up	2.325	9.021E-04
Fbp2	fructose bisphosphatase 2	Up	2.306	6.830E-03
Cyp4a12b	cytochrome P450, family 4, subfamily a, polypeptide 12B	Up	2.270	3.529E-02
Vnn1	vanin 1	Up	2.195	9.278E-03
Hsph1	heat shock 105kDa/110kDa protein 1	Up	2.194	3.778E-03
Nkain1	Na+/K+ transporting ATPase interacting 1	Up	2.122	2.779E-02
Kif20b	kinesin family member 20B	Up	2.104	3.800E-02

* Genes listed have expression changes over 2 fold and statistical significance of FDR corrected *p* value less than 0.05. Source data: Appendix Table 5.

Table 35. Differentially Expressed Genes Female day 2 at 1000 mg/kg (sponsor's table)

Gene Symbol	Gene Name	Direction	Fold Change	FDR *p* value
Gjb4	gap junction protein, beta 4	Down	44.676	2.695E-02
Ttr	transthyretin	Down	11.747	9.975E-05
Gbp6	guanylate binding protein 6	Down	6.045	2.695E-02
Dpys	dihydropyrimidinase	Up	52.041	5.728E-04
Aim1l	absent in melanoma 1-like	Up	6.207	4.020E-02
Mosc1		Up	5.535	2.695E-02
Angptl4	angiopoietin-like 4	Up	4.808	3.599E-09
Pdk4	pyruvate dehydrogenase kinase, isoenzyme 4	Up	4.774	3.572E-09
Aldh1a7	aldehyde dehydrogenase family 1, subfamily A7	Up	4.680	6.321E-04
Lbp	lipopolysaccharide binding protein	Up	4.410	5.687E-05
C3	complement component 3	Up	4.186	6.114E-08
Cyp4a12b	cytochrome P450, family 4, subfamily a, polypeptide 12B	Up	4.139	3.257E-02
Cyp24a1	cytochrome P450, family 24, subfamily a, polypeptide 1	Up	2.987	2.695E-02
Acsf2	acyl-CoA synthetase family member 2	Up	2.570	2.695E-02
Acot2	acyl-CoA thioesterase 2	Up	2.363	7.811E-03

* Genes listed have expression changes over 2 fold and statistical significance of FDR corrected *p* value less than 0.05. Source data: Appendix Table 6.

Table 36. Differentially Expressed Genes Male Day 8 at 1000 mg/kg (sponsor's table)

Gene Symbol	Gene Name	Direction	Fold Change	FDR p value
Anxa13	annexin A13	Down	5.775	2.216E-02
Hdc	histidine decarboxylase	Down	4.179	1.567E-03
Inmt	indolethylamine N-methyltransferase	Down	3.174	6.263E-06
Cndp1	carnosine dipeptidase 1 (metallopeptidase M20 family)	Down	2.736	6.754E-06
Vwa1	von Willebrand factor A domain containing 1	Down	2.694	4.179E-03
C4a	complement component 4A (Rodgers blood group)	Down	2.507	1.494E-02
Lipo1	lipase, member O1	Down	2.454	4.844E-03
Prss22	protease, serine, 22	Up	28.666	2.768E-02
Grem2	gremlin 2 homolog, cysteine knot superfamily	Up	10.131	4.078E-06
Cyp4a14	cytochrome P450, family 4, subfamily a, polypeptide 14	Up	9.341	7.665E-06
Cyp2a5	cytochrome P450, family 2, subfamily a, polypeptide 5	Up	3.221	1.567E-03
Hmgcs2	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2	Up	2.940	2.517E-02
Cish	cytokine inducible SH2-containing protein	Up	2.731	1.567E-03
Cryab	crystallin, alpha B	Up	2.700	1.036E-02
4930572J05 Rik	Them6 thioesterase superfamily member 6	Up	2.328	3.257E-02
Aqp4	aquaporin 4	Up	2.319	2.513E-02
Per2	period circadian clock 2	Up	2.285	2.897E-02

* Genes listed have expression changes over 2 fold and statistical significance of FDR corrected *p* value less than 0.05. Source data: Appendix Table 7.

Table 37. Differentially Expressed Genes Female Day 8 at 1000 mg/kg (sponsor's table)

Gene Symbol	Gene Name	Direction	Fold Change	FDR *p* value
Ttr	transthyretin	Down	16.571	4.204E-07
Npas2	neuronal PAS domain protein 2	Down	6.760	1.423E-03
A2m	alpha-2-macroglobulin	Down	5.255	2.685E-02
Pdk4	pyruvate dehydrogenase kinase, isoenzyme 4	Down	3.626	2.441E-03
Chi3l4	chitinase 3-like 4	Up	57.802	1.772E-05
Car3	carbonic anhydrase 3	Up	4.265	2.217E-02
Ren1	renin 1 structural	Up	2.584	1.499E-02

* Genes listed have expression changes over 2 fold and statistical significance of FDR corrected *p* value less than 0.05. Source data: Appendix Table 8.

Table 38. Differentially Expressed Genes Female Day 8 at 1000 mg/kg (sponsor's table)

Gene Symbol	Gene Name	Direction	Fold Change	FDR *p* value
Ttr	transthyretin	Down	16.571	4.204E-07
Npas2	neuronal PAS domain protein 2	Down	6.760	1.423E-03
A2m	alpha-2-macroglobulin	Down	5.255	2.685E-02
Pdk4	pyruvate dehydrogenase kinase, isoenzyme 4	Down	3.626	2.441E-03
Chi3l4	chitinase 3-like 4	Up	57.802	1.772E-05
Car3	carbonic anhydrase 3	Up	4.265	2.217E-02
Ren1	renin 1 structural	Up	2.584	1.499E-02

* Genes listed have expression changes over 2 fold and statistical significance of FDR corrected *p* value less than 0.05. Source data: Appendix Table 8.

Gender Differences

Kidney cortex samples collected at day 2 were compared from the male and female vehicle-treated CD-1 mice without exposure to empagliflozin. Male to female differences in gene expression were observed in drug metabolism, transporter proteins and ion channel proteins. Cytochrome P450 genes were either exclusively expressed in males (Cyp2j13, 4a12, and 7b1)or had higher expression in males (Cyp5, 24a1, 2d9, 2e1,4a12 and 4b1) or were more highly expressed in females compared to males (Cyp26b1, 2a5, 2c44, 2d112, 2d22, 2d26 and 4a14). In addition, glutathione detoxification genes (GSTA1, A2, A3, GST01 and MGST1) were more highly expressed in the female mouse kidney than the males (see Appendix for a tabulated list).

Toxicokinetics/Dosing Solution Analysis

Not assessed.

A 13 Week Renal Pathogenesis Study with BI 10773 in CD-1 Mice (Study# 12R139, U13-3467-01, non-GLP)

Reviewer note: The current study (study# 12R139, U13-3467-01) was conducted in male and female CD-1 mice with empagliflozin (BI 10773) at 0, 100, 300 and 1000 mg/kg for 13 weeks with interim (10/sex/group) sacrifices at weeks 1, 2, 4, 8. The purpose of the study was to evaluate kidney function as this was only tissue evaluated for histopathology, immunohistochemistry and genomic analysis in animals that reached their sacrifice dates. As the sponsor has previously conducted a 13-week study in male and female CD-1 mice, with empagliflozin at 0, 500, 750 and 1000 kg/kg (study# 07R169, U09-3067-01), the current 13-week study is summarized here to identify notable difference between the 2 study studies. Study# 07R169, U09-3067-01 was reviewed as part of the empagliflozin NDA (NDA 204629, finalized in DARRTS 11.05.2013).

Key Findings

Mortality occurred in one 1000 mg/kg female at day 8 and one 1000 mg/kg male at day 8. Three male and one female at 1000 mg/kg were moribund sacrificed within the first 10 days. One 1000 mg/kg male was moribund sacrificed at day 71. At days 30 and 63, respectively, one control male and 100 mg/kg female were also moribund sacrificed.

At necropsy the moribund sacrificed 1000 mg/kg animals were found with cecum gaseous abnormal contents and red discoloration. This is suggestive of malabsorption of glucose related to the off-target inhibition of SGLT-1 by empagliflozin.

BUN was significantly increased (9-35%) in the 100 and 1000 mg/kg males on day 15 and 92. BUN was also increased 6-32% on various days throughout the treatment period. **Reviewer note: This is likely due to increased protein catabolism as a consequence of caloric loss due glucosuria, which is a known pharmacodynamic consequence of SGLT2 inhibition.**

Urine glucose, volume, urine osmolality and urine electrolytes (sodium, potassium, chloride, calcium and phosphorus) were all increased in all treatment groups. These are expected secondary pharmacodynamics changes as a result of osmotic diuresis due to glycosuria.

Urine biomarkers cystatin C, mNGAL, clusterin, KIM-1 and microalbumin were significant increased but showed variability across the treatment groups and duration of the study. When adjusted for creatinine clearance, mNGAL, clusterin and microalbumin were increased approx. 2-6-fold. Reviewer note: **clusterin and microalbumin are freely filtered at the glomerulus, reabsorbed but not secreted. The presence of these urinary biomarkers suggests renal tubular injury.**

Plasma PTH was significantly decreased at the 2 hour time point a day 85 at ≥ 100 mg/kg. This is suggestive as a phosphate sparing mechanism due to osmotic diuresis.

Significantly increased kidney weight (absolute, body/brain weight ratio) were observed throughout the study in the empagliflozin treated females but this was without a histopathology correlation.

Microscopic kidney findings in the outer cortex were present in the 1000 mg/kg males. These were initially observed at day 29 and consisted of minimal cell necrosis and minimal increases in mitotic figures. The incidence of these findings increased on days 56 and 92. On day 56 minimal to mild karomegaly and minimal proximal tubule epithelial cell hyperplasia were present. The incidence (all treated 1000 mg/kg males) and severity (mild) of karyomegaly increased on day 92. In addition, the incidence of minimal proximal tubule epithelial cell hyperplasia also increased at day 92. These histopathology changes did not correlate with a change in organ weight or serum chemistry.

In the superficial cortex, the proliferation marker Ki-67 was noted on days 56 and 92 in the 1000 mg/kg males. Ki-67 staining was present in the same region of the kidney as the observed kidney tubular hyperplasia and increased mitoses.

Baseline non-treatment (vehicle-treated) gender differences in gene expression for the kidney cortex were observed at week one. The differentially expressed genes included drug metabolism, transporters and ion channels. In addition, glutathione-mediated detoxification genes were more highly expressed in female CD-1 mice and the UDGPT enzymes were more highly expressed in male CD-1 mice. These differences are consistent with the known gender differences in mammalian drug metabolism.

Treatment with empagliflozin for 8 weeks resulted in the modulation of gene expression in genes related to drug metabolism (CYP450), complement system and p53 regulation in the 1000 mg/kg males relative to the vehicle-treated groups.

Treatment with empagliflozin for 13 weeks resulted in the modulation of gene expression in genes related to renal cell development and function (cystogenesis and fibrosis), cell cycle regulation (p53), cell proliferation, cell to cell signaling, cell adhesion and cytoskeleton structure in the 1000 mg/kg males relative to the vehicle-treated groups. Of note also increased were genes related to oxidative stress, renal injury biomarker (KIM-1) and cell proliferation marker Mki67.

Male and female CD-1 were treated with empagliflozin at 100, 300 and 1000 mg/kg. T_{max} was between 1-2 hr and exposure (AUC_{0-24}) was dose-proportional. Exposure in females at 300 and 1000 mg/kg was increased approx. 2-fold relative to males.

Male CD-1 mice treatment with empagliflozin at 100, 300 and 1000 mg/kg corresponds to 6x, 19x and 71x the maximum recommended dose (MRHD) of the 25 mg clinical exposure. Female CD-1 mice treatment with empagliflozin at 100, 300 and 1000 mg/kg corresponds to 8x, 30x and 153x the maximum recommended dose (MRHD) of the 25 mg clinical exposure.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Bacterial Reverse Mutation Assay

Study no.:	U13-3656-01
Study report location:	eCTD SN 26
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	July 17th 2013
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	BI00737687 (M466/2), 102950-038 and 99.2%

Key Study Findings

M466/2 (BI00737687) was not mutagenic in S. typhimurium and E. coli strains in the Ames assay using the plate incorporation method.

(b) (4) [redacted]

Study Validity

(b) (4) [redacted]

Results

M466/2 (BI00737687) did not increase the number of revertants with and without metabolic activation (see sponsor's tabled below).

Table 39. Ames Assay for M466/2 Without Metabolic Activation (sponsor's table)

Test Article Id : BI00737687
Study Number : AD75YJ.501028.BTL
Experiment No : B1

Average Revertants Per Plate ± Standard Deviation

Activation Condition : None

Dose (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 *uvr* A
Vehicle	25 ± 5	91 ± 13	9 ± 4	5 ± 2	33 ± 10
39.3	20 ± 4	72 ± 5	9 ± 1	5 ± 3	38 ± 9
78.5	29 ± 11	83 ± 12	12 ± 3	7 ± 3	39 ± 3
157	23 ± 7	96 ± 5	14 ± 1	7 ± 5	39 ± 6
313	22 ± 10	92 ± 8	10 ± 5	3 ± 1	44 ± 7
625	22 ± 6	82 ± 9	11 ± 2	2 ± 2	62 ± 7
1250	25 ± 9	66 ± 7	10 ± 2	5 ± 1	51 ± 9
2500	4 ± 4	56 ± 8	5 ± 1	3 ± 1	52 ± 2
5000	2 ± 3	6 ± 4	1 ± 1	0 ± 1	33 ± 5
Positive	84 ± 4	660 ± 88	357 ± 14	404 ± 39	270 ± 26

Activation Condition : Rat Liver S9

Dose (µg/plate)	TA98	TA100	TA1535	TA1537	WP2 *uvr* A
Vehicle	16 ± 6	89 ± 11	16 ± 3	6 ± 4	44 ± 6
39.3	16 ± 9	85 ± 5	16 ± 2	9 ± 3	52 ± 7
78.5	19 ± 6	92 ± 12	15 ± 2	5 ± 2	55 ± 10
157	16 ± 1	91 ± 15	11 ± 6	6 ± 3	47 ± 2
313	10 ± 5	96 ± 5	17 ± 3	7 ± 2	48 ± 13
625	7 ± 4	76 ± 13	13 ± 4	4 ± 1	50 ± 8
1250	5 ± 2	71 ± 7	10 ± 2	7 ± 3	55 ± 3
2500	4 ± 0	61 ± 6	10 ± 4	6 ± 2	71 ± 10
5000	5 ± 3	32 ± 7	8 ± 8	7 ± 3	51 ± 9
Positive	262 ± 17	412 ± 22	61 ± 6	48 ± 6	157 ± 19

Vehicle = Vehicle Control
Positive = Positive Control (50 µL plating aliquot)
Plating aliquot = 50 µL

7.2 *In Vitro* Assays in Mammalian Cells

In Vitro Mammalian Cell Micronucleus Screening Assay in Chinese Hamster Ovary (CHO) Cells Under Three Treatment Conditions

Study no.:	13R097, U13-3655-01
Study report location:	eCTD SN 0026, SDN 0027
Conducting laboratory and location:	(b) (4)
Date of study initiation:	16th July 2013
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	BI00737687 (M466/2), 102950-038 and 99.2%

Key Study Findings

In the in vitro micronucleus assay, BI00737687 (metabolite M466/2) produced statistically significant micronuclei in CHO cells in the 24 hr treatment group without metabolic activation (S9).

Methods

(b) (4)

Study Validity

(b) (4)

Results

Dose Range Finding Study

In the 4 hr treatment without S9 the highest dose selected for evaluation (15.8 mcg/mL) resulted in 50% cytotoxicity. M466/2 at 15.8 mcg/mL resulted in a significant increase in micronucleus formation. The next lower dose of 11.8 mcg/mL was not evaluated for micronucleus formation and thus dose responsiveness cannot be assessed (see sponsor's table below).

In the 4 hr treatment with S9 the highest dose selected for evaluation (118.7 mcg/mL) resulted in 51% cytotoxicity. No statistically significant micronuclei were formed (see sponsor's table).

In the 24 hr treatment without S9 the highest dose selected for evaluation (8.9 mcg/mL) resulted in 62% cytotoxicity. A statistically significant increase in micronuclei were observed at 8.9 mcg/mL and dose-responsive effect was not observed (see sponsor's table below).

Table 40. DRF CHO Cell Micronucleus Assay with Metabolite M466/2 (sponsor's table)

Treatment Condition (µg/mL)	CBPI[1]	Cytotoxicity[2] (%)	Percentage of MNBN[3] Cells/ Total BN[4] Cells Counted (%)
4-Hour Treatment -S9			
DMSO	1.798		4.3
2.1	1.724	9	4.2
2.8	1.732	8	§
3.8	1.720	10	§
5	1.706	12	§
6.7	1.686	14	§
8.9	1.672	16	4.0
11.9	1.530	34	§
15.8	1.398	50	6.2*
21.1	1.122	85	§
28.2	1.038	95	§
37.5	1.024	97	§
50.1	1.000	100	§
66.7	1.000	100	§
89	1.000	100	§
118.7	1.000	100	§
158.2	1.000	100	§
210.9	1.000	100	§
281.3	1.000	100	§
375	†	†	†
500	†	†	†
MMC, 0.1	1.574	28	§
MMC, 0.2	1.400	50	12.6**
4-Hour Treatment +S9			
DMSO	1.818		3.6
2.1	1.796	3	3.9
2.8	1.812	1	§
3.8	1.816	0	§
5	1.784	4	§
6.7	1.782	4	§
8.9	1.764	7	§
11.9	1.710	13	§
15.8	1.742	9	§
21.1	1.742	9	§
28.2	1.736	10	§
37.5	1.734	10	§
50.1	1.734	10	§
66.7	1.676	17	3.5
89	1.572	30	§
118.7	1.400	51	3.8
158.2	1.160	80	§
210.9	1.040	95	§
281.3	1.000	100	§
375	1.000	100	§
500	1.000	100	§
CP, 2.5	1.428	48	§
CP, 5	1.264	68	28.7**
CP, 7.5	1.226	72	§

[1] CBPI = Cytokinesis-Block Proliferation Index
[2] Relative to the solvent control
[3] MNBN = micronucleated binuclear
[4] BN = binucleated
DMSO = Dimethyl sulfoxide; CP = Cyclophosphamide
MMC = Mitomycin C
§ Dose levels were tested but not evaluated for MNBN Cells.
† Not scored due to excessive cytotoxicity
* p≤0.05, Fisher's exact test; ** p≤0.01, Fisher's exact test

Table 41. Table xx. Definitive CHO Cell Micronucleus Assay with Metabolite M466/2 [24hr – S9] (sponsor's table)

Treatment Condition (µg/mL)	CBPI[1]	Cytotoxicity[2] (%)	Percentage of MNBN[3] Cells/ Total BN[4] Cells Counted (%)
24-Hour Treatment –S9			
DMSO	1.832		3.8
2.1	1.778	6	4.3
2.8	1.682	18	4.0
3.8	1.678	19	§
5	1.672	19	§
6.7	1.490	41	4.3
8.9	1.318	62	7.9**
11.9	1.162	81	§
15.8	†	†	†
21.1	†	†	†
28.2	†	†	†
37.5	†	†	†
50.1	†	†	†
66.7	†	†	†
89	†	†	†
118.7	†	†	†
158.2	†	†	†
210.9	†	†	†
281.3	†	†	†
375	†	†	†
500	†	†	†
VB, 5 ng/mL	1.804	3	
VB, 10 ng/mL	2.048	-26	25.6**

[1] CBPI = Cytokinesis-Block Proliferation Index
[2] Relative to the solvent control
[3] MNBN = micronucleated binuclear
[4] BN = binucleated
DMSO = Dimethyl sulfoxide
VB = Vinblastine
§ Dose levels were tested but not evaluated for MNBN Cells.
† Not scored due to excessive cytotoxicity

* p≤0.05, Fisher's exact test; ** p≤0.01, Fisher's exact test
Cochran-Armitage Trend Test for Dose Response Significant for without activation (4-hour); Critical Chi-Square (p≤0.05): 7.82 Chi-Square: 3.93
Cochran-Armitage Trend Test for Dose Response Significant for without activation (24-hour); Critical Chi-Square (p≤0.05): 9.49 Chi-Square: 15.54

Definitive Study

In the 4 hr treatment without S9 the highest dose selected for evaluation (16 mcg/mL) resulted in 51% cytotoxicity. M466/2 at16 mcg/mL did not result in a significant increase in micronucleus formation. The next lower dose of 15 mcg/mL was not evaluated for micronucleus formation and thus dose responsiveness cannot be assessed (see sponsor's table below).

In the 24 hr treatment without S9 the highest dose selected for evaluation (10 mcg/mL) resulted in 66% cytotoxicity. A statistically significant increase in micronuclei were observed at 8.5, 9 and 10 mcg/mL and a dose-responsive effect was observed (see sponsor's table below). Cytotoxicity at 8.5, 9 and 10 mcg/mL were 41%, 51% and 66%,

respectively. Thus, the micronuclei formation at 10 mcg/mL are considered to be an artifact of cytotoxicity.

Table 42. Definitive CHO Cell Micronucleus Assay with Metabolite M466/2 (sponsor's table)

Treatment Condition (µg/mL)	CBPI[1]	Cytotoxicity[2] (%)	Percentage of MNBN[3] Cells/ Total BN[4] Cells Counted (%)
4-Hour Treatment -S9			
DMSO	1.740		4.6
2.5	1.770	-4	§
5	1.746	-1	§
10	1.704	5	3.6
12	1.638	14	§
13	1.594	20	3.1
14	1.494	33	4.2
15	1.498	33	§
16	1.364	51	5.2
18	1.196	74	§
20	1.186	75	§
MMC, 0.1	1.646	13	§
MMC, 0.2	1.554	25	17.8**
24-Hour Treatment –S9			
DMSO	1.936		4.2
2.5	1.912	3	3.6
5	1.778	17	4.3
6.5	1.614	34	§
7	1.638	32	§
7.5	1.678	28	§
8	1.614	34	§
8.5	1.549	41	6.2*
9	1.454	51	9.0**
9.5	1.454	51	§
10	1.316	66	6.2*
VB, 5 ng/mL	1.898	4	10.3**
VB, 10 ng/mL	1.996	-6	§

[1] CBPI = Cytokinesis-Block Proliferation Index
[2] Relative to the solvent control
[3] MNBN = micronucleated binuclear
[4] BN = binucleated
DMSO = Dimethyl sulfoxide
MMC = Mitomycin C; VB = Vinblastine
§ Dose levels were tested but not evaluated for MNBN Cells.

* p≤0.05, Fisher's exact test; ** p≤0.01, Fisher's exact test
Cochran-Armitage Trend Test for Dose Response Significant for without activation (24-hour); Critical Chi-Square (p≤0.05): 9.49 Chi-Square: 28.83

7.4 Other Genetic Toxicity Studies

Bioanalysis of M466/2 (BI00737687) and M380/1 in Bacteria Reverse Mutation Assay Test Media Using Authentic Standard (Study# U13-3895-01)

Method

The sponsor conducted a "simulated Ames plate incubation assay" without the bacteria as follows: A mixture of 0.6% top agar, M466/2 (39.3, 157, 625 and 1250 mcg/plate) or PBS (sham assay) (in triplicate) was prepared and 0.5 mL aliquot of these preparations were placed in 50 mL Falcon tubes. Each mixture was then placed in an incubator at 37°C for 48 hrs. Following the incubation each, mixture was manually homogenized with a pestle and a quench solution (acentonitrile containing 1uM $^{13}C_6$-BI 10773 (internal standard) and 0.1% acetic acid) was added. Following further extraction the formation, of metabolites was determined using LC/MS/MS. M466/2 and M380/1 were used as authentic standards.

Results

Under the conditions of the assay the empagliflozin metabolite M466/2 degraded to metabolite M380/1. M380/1 was the major metabolite in the mixture at approx. 79-92% (see sponsor's table below). **Reviewer note: the formation of M380/1 was evaluated in the absence of the bacterial strains and a metabolic activation system (i.e. S9). This implies that metabolite M466/2 is very labile and degrades to metabolite M380/1.**

Table 43. Metabolite M466/2 Degradation Following Incubation in Top Agar (sponsor's table)

Dosed M466/2 µg/plate	Dosed [M466/2] µM	Replicate #	Measured [M466/2] µM	Measured [M380/1] µM	% of M380/1 formed	% of M380/1 formed (mean±SD)	% of remaining M466/2	% of M466/2 remaining (mean± SD)
39.3	1.67	1	0.154	1.52	90.8	91.5 ± 0.749	9.20	8.47 ± 0.749
		2	0.121	1.45	92.3		7.70	
		3	0.185	1.99	91.5		8.50	
157	6.66	1	0.804	8.37	91.2	91.1 ± 0.149	8.76	8.94 ± 0.149
		2	0.726	7.32	91.0		9.02	
		3	0.717	7.23	91.0		9.02	
625	26.6	1	3.39	27.2	88.9	88.8 ± 0.102	11.1	11.2 ± 0.102
		2	3.87	30.6	88.8		11.2	
		3	3.75	29.5	88.7		11.3	
1250	106	1	37.5	122	76.5	79.0 ± 7.68	23.5	21.0 ± 7.68
		2	35.1	94.4	72.9		27.1	
		3	15.4	109	87.6		12.4	

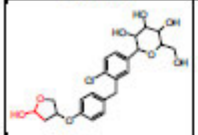
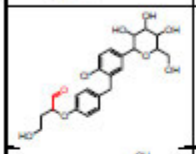
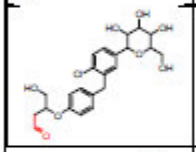
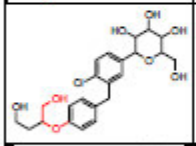
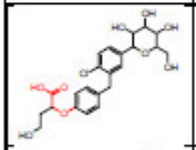
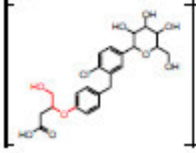
Structure-Toxicity-Relationship Assessment of BI 10773 M466 Metabolites (Study# 13R084, U13-3469-01, non-GLP)

Method
Computational analysis (Lhasa DEREK, MultiCASE and CASE Ultra) was conducted with [male mouse predominant] empagliflozin metabolites M466(2), aldehydes A and B and downstream metabolites M482/1, M482/2 and M468/1. Public domain databases were searched for compounds with structural similarity and to identify compounds with toxicity data using Leadscope.

Results
Analysis of empagliflozin (BI 10773) metabolites analysis using DEREK identified a genotoxicity structural alert for an alkyl aldehyde or aldehyde precursor in the structure of M466(2) and aldehyde B which was suggestive of chromosome damage and mutagenicity in vitro (see sponsor's table below). DEREK also identified a genotoxicity structural alert for an aldehyde precursor in M466(2), aldehyde A and aldehyde B, which was suggestive of skin sensitization (see sponsor's table below).

DEREK also identified a structural alert for a beta o/s-substituted carboxylic acid precursor synonymous with peroxisome proliferation for aldehyde A, B and metabolites M468/1, M482/1 and M482/2 (see sponsor's table below). **Reviewer note: some prototypical peroxisome proliferators cause a unique histopathological observation in the outer stripe of the outer medulla renal tubules described as simple hyperplasia[#]. The incidence and severity of renal cystic hyperplasia was dose dependently increased in chronically treated (2 year) male mice and atypical renal tubular hyperplasia was also increased at the high dose in the same mice. However, these lesions are in the cortex as opposed to the medullary location of the kidney histopathology of the peroxisome proliferators. Thus the relevance of the structural alert for the empagliflozin metabolites is of questionable significance.**

Table 44. Structure Activity Relationship Analysis(sponsor's table)

Structure	Compound	DEREK Alert 1	DEREK Alert 2	DEREK Alert 3	Leadscope	MCASE
	M466(2)	Alkyl aldehyde or precursor: Genotoxicity (chromosome damage, mutagenicity in vitro)	Aldehyde precursor: Skin sensitization		NEG/Not in domain for standard genotoxicity tests. No similar compounds in database.	NEG
	Aldehyde A		Aldehyde: Skin sensitization	Beta O/S-substituted carboxylic acid or precursor: Peroxisome proliferation	NEG/Not in domain for standard genotoxicity tests. No similar compounds in database.	NEG
	Aldehyde B	Alkyl aldehyde or precursor: Genotoxicity (chromosome damage, mutagenicity in vitro)	Aldehyde: Skin sensitization	Beta O/S-substituted carboxylic acid or precursor: Peroxisome proliferation	NEG/Not in domain for standard genotoxicity tests. No similar compounds in database.	NEG
	M468/1			Beta O/S-substituted carboxylic acid or precursor: Peroxisome proliferation	NEG/Not in domain for standard genotoxicity tests. No similar compounds in database.	NEG
	M482/1			Beta O/S-substituted carboxylic acid or precursor: Peroxisome proliferation	NEG/Not in domain for standard genotoxicity tests. No similar compounds in database.	NEG
	M482/2			Beta O/S-substituted carboxylic acid or precursor: Peroxisome proliferation	NEG/Not in domain for standard genotoxicity tests. No similar compounds in database.	NEG

Structural alerts for these metabolites were not identified in MultiCASE, CASE Ultra or Leadscope (see sponsor's table above).

[#]Ozaki K, et al.,: Toxiologic Pathology: 29: 440-501 (2001).

11 Integrated Summary and Safety Evaluation

NDA 204629 efficacy supplement 005 was submitted to the NDA under SDN 0055 to evaluate clinical study 1276.1. (b) (4)

[redacted]

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Safety Pharmacology
With the use of in vitro safety pharmacology screens, empagliflozin was found to have low affinity binding, suggesting low potential for activity at the receptors, ion channels or transporters examined and for the human kinome. Of note, empagliflozin was the least reactive of the SGLT2 inhibitors examined in this assay in the order canagliflozin>> LX-4211 > ipragliflozin> dapagliflozin = sergliflozin > empagliflozin = remigliflozin = tofogliflozin.

PK/ADME
Oral administration of radiolabeled empagliflozin in CD-1 mice showed the majority of radioactivity to be distributed in the liver and kidney over the time course of the study (12 hours). Exposure relative to the blood was generally highest in the liver, followed by the kidney and lung, suggesting highly perfused tissues are exposed to empagliflozin. The half-life in tissues was generally 2-3 hours

Probe specific transport inhibitors showed empagliflozin was actively transported into rat and mouse kidney slices predominantly by SGLT transporters followed by OAT3 transporters. The uptake into the rat and mouse kidney slices was concentration-dependent and saturable. Further in vitro characterization of empagliflozin transport in vesicular transport studies using xenopus laevis oocytes showed empagliflozin to be a substrate of rat Oat3, Oatp1a1, mouse oatp1a1, oat3 and human SGLT2 transporters. The uptake of empagliflozin was time- and concentration-dependent.

In vitro metabolism studies with mouse, rat and human kidney and liver microsomes showed the most activity with regards to empagliflozin breakdown and formation of metabolite M466/2 to occur predominantly with male mouse kidney microsomes. Female kidney microsomes, mouse liver microsomes (male and female), rat liver microsomes (male and female), showed limited metabolism of empagliflozin to form metabolite M466/2. In contrast, incubation of empagliflozin with human liver microsomes did not result in the formation of metabolite M466/2 but yielded a glucuronide metabolite M626/1, which was also formed with male mouse liver microsomes. Metabolite M466/2 was formed at a 21-fold lower extent in the human kidney (medulla) microsomes relative to male mouse kidney microsomes.

In mouse kidney subcellular fractions, M466/2 was also produced with S9 and kidney cytosol as minor metabolites but to a much lower extent than with kidney microsomes alone. Mouse kidney S9, cytosol, microsomes alone or in combination also produced metabolites M688/1, M380/1 and M464/1, suggestive of further metabolites and downstream processing of empagliflozin.

Metabolite M466/2 was found to stoichiometrically degrade to metabolite M380/1 (82%) and with minimal degradation to a 4-hydroxycrotoaldehyde metabolite that was trapped with glutathione (18%)

Treatment of CD-1 mice with a single dose of empagliflozin at 1000 mg/kg also identified metabolites M688/1, M380/1 and M464/1 as being formed by the kidneys in vivo. However, the male mouse kidney metabolized empagliflozin predominantly to metabolite M482/1 and at a 2-fold higher extent that the female mouse kidney. Metabolites M688/1, M380/1 and M464/1 were produced at 10-20% in male kidneys but less than 10% in the female mouse kidney, thus corroborating the in vitro gender differences in the kidney metabolism of empagliflozin.

Empagliflozin was shown to be not directly cytotoxic or mitogenic to mouse renal epithelial cells in vitro.

General Toxicology
Pivotal repeat dose studies were in CD-1 mice treated with empagliflozin for 7 days and for up to 13-weeks. The empagliflozin exposure was 6-153x MRHD (25 mg) in the 13-week mouse study.

Findings in the pivotal mouse studies were generally consistent with the pharmacodynamic activity of empagliflozin, including reduced body weight, glucosuria, polyuria, osmotic diuresis, and electrolyte losses, as has been previously described in this species. Of note, urinary biomarkers clusterin, microalbumin, KIM-1 and MNGAL were increased, suggestive of renal injury. In addition, the enriched kidney cortex genomic analysis showed baseline (un-treated) gene expression differences in male and female CD-1 mice, in particular for metabolism enzymes and glutathione detoxification enzymes.

Genotoxicity
The empagliflozin metabolite M466/2 in a simulated Ames assay without the bacterial strains or metabolic activation showed the spontaneous degradation of M466/2 to metabolite M380/1, showing the very labile nature of M466/2. Evaluation of metabolite M466/2 in a standard in vitro Ames showed metabolite M466/2 was not mutagenic. However, metabolite M466/2 was found to induce micronuclei in the in vitro CHO cell assay, at 24 hours post-dose without metabolic activation, with a dose-response effect. M466/2 is minimally formed in human kidney in vitro (21-fold lower compared to the mouse kidney) and not observed in vivo, thus metabolite M466/2 is unlikely to be a risk to humans.

Computational structure activity relationship evaluation of metabolite M466/2 identified a structural alert(s) for metabolite M466/2. However, as metabolite M466/2 was negative in the AMES assay and showed equivocal findings in the in vitro micronucleus assay no further genotoxicity assessment is required.


(b) (4)

12 Appendix/Attachments

A 7 Day Renal Function and Toxicity Study With BI 10773 in CD-1 Mice (Study # U13-3465-01 (12r144))

Table 46. Renal Genes Analyzed (sponsor's table)

Function	Gene Symbol	Gene Name
Apoptosis	Clu	clusterin
	Myc	myelocytomatosis oncogene
	Nfkb1	nuclear factor of kappa light polypeptide gene enhancer in B cells 1, p105
	Nrip1	nuclear receptor interacting protein 1
	Rac1	RAS-related C3 botulinum substrate 1
	Rac2	RAS-related C3 botulinum substrate 2
	Rhoq	ras homolog gene family, member Q
Calcuim homeostasis	Sp1	trans-acting transcription factor 1
	Trpv4	transient receptor potential cation channel, subfamily V, member 4
	Trpv5	transient receptor potential cation channel, subfamily V, member 5
	Trpv6	transient receptor potential cation channel, subfamily V, member 6
Cell cycle and proliferation	Axl	AXL receptor tyrosine kinase
	Cdc42	cell division cycle 42
	Cdk1	cyclin-dependent kinase 1
	Cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)
	Pcna	proliferating cell nuclear antigen
	Pik3ap1	phosphoinositide-3-kinase adaptor protein 1
	Fos	FBJ osteosarcoma oncogene
	Foxo1	forkhead box O1
	Foxo3	forkhead box O3
	Igfbp3	insulin-like growth factor binding protein 3
	Jun	Jun oncogene
	Mtor	mechanistic target of rapamycin (serine/threonine kinase)
	Scube1	signal peptide, CUB domain, EGF-like 1

Table 46. Renal Genes Analyzed (sponsor's table) continued

Function	Gene Symbol	Gene Name
Chemokine	Ccl2	chemokine (C-C motif) ligand 2
	Cxcr4	chemokine (C-X-C motif) receptor 4
ER stress	Hspa5	heat shock protein 5
	Scamp2	secretory carrier membrane protein 2
Cell adhesin and fibrosis	Akap12	A kinase (PRKA) anchor protein (gravin) 12
	Ctgf	connective tissue growth factor
	Eno2	enolase 2, gamma neuronal
	Serpine1	serine (or cysteine) peptidase inhibitor, clade E, member 1
Hypoxia signaling	Hyou1	hypoxia up-regulated 1
Early Injury Response	Egr1	early growth response 1
Lipid metabolism	Hnf4a	hepatic nuclear factor 4, alpha
	Srebf2	sterol regulatory element binding factor 2
NO signaling	Adm2	adrenomedullin 2
	Hp	haptoglobin
	Mt1	metallothionein 1
	Mt2	metallothionein 2
	Nos2	nitric oxide synthase 2, inducible
Oxidative stress	Keap1	kelch-like ECH-associated protein 1
	Nfe2l2	nuclear factor, erythroid derived 2, like 2
Transport activity	Atp1a1	ATPase, Na+/K+ transporting, alpha 1 polypeptide
	Atp2b1	ATPase, Ca++ transporting, plasma membrane 1
	Slc22a1	solute carrier family 22 (organic cation transporter), member 1
	Slc22a12	solute carrier family 22 (organic anion/cation transporter), member 12
	Slc22a2	solute carrier family 22 (organic cation transporter), member 2
	Slc22a6	solute carrier family 22 (organic anion transporter), member 6
	Slc22a8	solute carrier family 22 (organic anion transporter), member 8
	Slc25a30	solute carrier family 25, member 30
	Slc2a1	solute carrier family 2 (facilitated glucose transporter), member 1
	Slc2a2	solute carrier family 2 (facilitated glucose transporter), member 2
	Slc35b4	solute carrier family 35, member B4
	Slc4a4	solute carrier family 4 (anion exchanger), member 4
	Slc5a1	solute carrier family 5 (sodium/glucose cotransporter), member 1

Table 47. Renal Genes Analyzed (sponsor's table)

Function	Gene Symbol	Gene Name
Transport activity	Slc5a10	solute carrier family 5 (sodium/glucose cotransporter), member 10
	Slc5a2	solute carrier family 5 (sodium/glucose cotransporter), member 2
	Slc5a8	solute carrier family 5 (iodide transporter), member 8
	Slc8a1	solute carrier family 8 (sodium/calcium exchanger), member 1
	Slco1a1	solute carrier organic anion transporter family, member 1a1

Table 48. Female CD-1 Mice Baseline Upregulated Genes Compared to Male Mouse (sponsor's table)

Gene Symbol	Gene Name	Fold Change (F/M)
Xist	inactive X specific transcripts	>500
Slc7a12	solute carrier family 7 (cationic amino acid transporter, y+ system), member 12	278.76
BC018473	cDNA sequence BC018473	242.35
Tmprss6	transmembrane serine protease 6	214.84
Serpina6	serine (or cysteine) peptidase inhibitor, clade A, member 6	135.03
Slc17a2	solute carrier family 17 (sodium phosphate), member 2	126.85
Cacna1i	calcium channel, voltage-dependent, alpha 1I subunit	101.48
Atp13a4	ATPase type 13A4	97.84
Prlr	prolactin receptor	72.10
Fabp1	fatty acid binding protein 1, liver	55.53
Bhmt	betaine-homocysteine methyltransferase	43.83
Myh1	myosin, heavy polypeptide 1, skeletal muscle, adult	43.06
Apol10b	apolipoprotein L 10B	36.26
Abcc3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	35.44
Slc22a29	solute carrier family 22. member 29	35.10
Rdh19	retinol dehydrogenase 19	33.84
Spata20	spermatogenesis associated 20	31.32
H2-Ea-ps	histocompatibility 2, class II antigen E alpha, pseudogene	28.78
4932425I24Rik	Mycbp-associated, testis expressed 1	25.61
Igf2	insulin-like growth factor 2	23.61
Gbp6	guanylate binding protein 6	23.57
Kynu	kynureninase (L-kynurenine hydrolase)	22.33
Gm10639	predicted gene 10639	21.82
Ifitm7	interferon induced transmembrane protein 7	20.37
Gltpd2	glycolipid transfer protein domain containing 2	20.24
Cited1	Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 1	18.57
Baat	bile acid-Coenzyme A: amino acid N-acyltransferase	15.98
Cpn1	carboxypeptidase N, polypeptide 1	13.90
Gsta2	glutathione S-transferase, alpha 2 (Yc2)	13.74
Thbs4	thrombospondin 4	13.48
Gsta1	glutathione S-transferase, alpha 1 (Ya)	12.86
Gc	group specific component	12.13
Dfnb59	deafness, autosomal recessive 59 (human)	11.44
Scd1	stearoyl-Coenzyme A desaturase 1	10.85
Col17a1	collagen, type XVII, alpha 1	10.79
4931408A02Rik	eva-1 homolog C	10.73
Ceacam2	carcinoembryonic antigen-related cell adhesion molecule 2	10.43
Arsi	arylsulfatase i	10.19
Kcna1	potassium voltage-gated channel, shaker-related subfamily, member 1	10.15
Gm221	Coiled-coil domain containing 170	10.15

*F: Female, M: Male. Genes listed have over 5 fold expression difference and statistical significance of FDR corrected $p<0.05$. Appendix Table 9

Table 48. Female CD-1 Mice Baseline Upregulated Genes Compared to Male Mouse –Continued (sponsor's table)

Gene Symbol	Gene Name	Fold Change (F/M)
2310008H04Rik	RIKEN cDNA 2310008H04 gene	9.67
Serpina10	serine (or cysteine) peptidase inhibitor, clade A10	9.63
Sytl3	synaptotagmin-like 3	9.55
Gbp3	guanylate binding protein 3	9.46
Cyp2d12	cytochrome P450, family 2, subfamily d, polypeptide 12	9.16
Sorcs2	sortilin-related VPS10 domain containing receptor 2	9.07
Kcne11	potassium voltage-gated channel, Isk-related family, member 1-like	8.89
Elovl6	ELOVL family member 6, elongation of long chain fatty acids (yeast)	8.71
9030619P08Rik	RIKEN cDNA 9030619P08 gene	8.37
Angptl3	angiopoietin-like 3	8.34
Ccr1	chemokine (C-C motif) receptor 1	8.23
Hsd17b14	hydroxysteroid (17-beta) dehydrogenase 14	8.08
Pcolce2	procollagen C-endopeptidase enhancer 2	7.51
Nup62cl	nucleoporin 62 C-terminal like	7.31
Acot7	acyl-CoA thioesterase 7	6.98
Padi4	peptidyl arginine deiminase, type IV	6.81
Cdh6	cadherin 6	6.59
Trim46	tripartite motif-containing 46	6.51
Insc	inscuteable homolog (Drosophila)	6.38
Tgtp1	T cell specific GTPase 1	6.30
Abcb1b	ATP-binding cassette, sub-family B (MDR/TAP), member 1B	6.22
Ugt2b34	UDP glucuronosyltransferase 2 family, polypeptide B34	6.18
Capg	capping protein (actin filament), gelsolin-like	5.98
Cbr1	carbonyl reductase 1	5.90
Plxdc1	plexin domain containing 1	5.85
Ly6f	lymphocyte antigen 6 complex, locus F	5.79
Naaladl1	N-acetylated alpha-linked acidic dipeptidase-like 1	5.54
Aadat	aminoadipate aminotransferase	5.51
Galr2	galanin receptor 2	5.50
2310007B03Rik	RIKEN cDNA 2310007B03 gene	5.33
Akr1c19	aldo-keto reductase family 1, member C19	5.23
Lgi2	leucine-rich repeat LGI family, member 2	5.23
Nxnl1	nucleoredoxin-like 1	5.18
Igtp	interferon gamma induced GTPase	5.18
Foxq1	forkhead box Q1	5.15
Marcksl1-ps4	MARCKS-like 1, pseudogene 4	5.14
D330045A20Rik	RIKEN cDNA D330045A20 gene	5.04

*F: Female, M: Male. Genes listed have over 5 fold expression difference and statistical significance of FDR corrected $p \leq 0.05$. Appendix Table 9

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/s/

MUKESH SUMMAN
02/19/2016

RONALD L WANGE
02/19/2016
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s005

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 204629/ NDA 206111
Supplement #:	Supplement 5/ supplement 1
Drug Name:	Jardiance (empagliflozin) / Synjardy (Empagliflozin and metformin hydrochloride)
Indication(s):	Type 2 Diabetes Mellitus
Applicant:	Boehringer Ingelheim Pharmaceuticals Inc
Date(s):	Stamp date: May 20, 2015/ September 11, 2015
	Primary review due date: February 11, 2016
	PFUFA :March 20, 2016 / July 11, 2016
Review Priority:	Standard
Biometrics Division:	Division of Biometric II
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Keywords: Missing data, multiplicity, sensitivity analysis

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1 EXECUTIVE SUMMARY

This is a statistical review for Boehringer Ingelheim's supplement application to its new drug applications (NDA 204629 or NDA 206111) for the treatment of concomitant therapy with empagliflozin and metformin in treatment –naïve patients with type 2 diabetes mellitus (T2DM). The applicant is seeking for approval of the revised draft labelling for Jardiance tablets and Synjardy (empagliflozin and metformin hydrochloride) based on study 1276.1. Jardiance is approved for use in adults with T2DM at the doses of 10 mg and 25 mg daily. Synjardy is approaved for use in adults with T2DM at the following twice daily doses: 5mg empagliflozin/500 mg metformin, 5 mg empagliflozin/1000 mg metformin, 12.5mg empagliflozin/500 mg metformin, 12.5mg empagliflozin/ 1000 mg metformin.

1.1 Conclusions and Recommendations

In study 1276.1, the combination uses of empagliflozin (12.5mg bid or 5 mg bid) and metformin (1000 bid or 500 mg bid) showed treatment effect in reducing HbA1c compared to monotherapy therapy (empagliflozin or metformin alone). The reductions in HbA1c from baseline at week 24 were statistically significant at the prespecified alpha level in the study.

1.2 Brief Overview of Clinical Studies

The supplement application included one study 1276.1 for supporting approval by regulatory authorities for empagliflozin and metformin FDC therapy as first line therapy in drug naïve patients with type 2 diabetes mellitus. The study was a 24-week phase III, randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin+metformin compared with the individual components of empagliflozin or metformin in drug-naïve patients with type 2 diabetes mellitus. Patients in the study were randomized to 8 treatment arms as the follow: empagliflozin12.5 mg bid+metformin 1000mg bid, empagliflozin 12.5 mg bid+ metformin 500mg bid, empagliflozin 5mg bid+ metformin 1000 mg bid, empagliflozin 5 mg bid + metformin 500 mg bid, empagliflozin 25 mg qd, empagliflozin 10 mg qd , metformin 1000 mg bid, metformin 500 mg bid. A hierarchical testing procedure was pre-specified to test for primary and key secondary endpoints.
After 24 weeks of treatment, the reduction of HbA1c (%) from baseline of twice daily oral administration of empagliflozin+metformin was -1.44 to -1.77. It has been shown that the combinations of empagliflozin+metformin were superior to the individual components (empagliflozin or metformin alone). The non-inferiority of empagliflozin alone over metformin was not established.

1.3 Statistical Issues and concerns

The main statistical issues were that the applicant did not conduct the analysis on an intent-to treatment population and the applicant did not perform sensitivity analysis to study the impact of the missing data.

The primary analysis proposed by applicant only includes data in patients who remained on treatment and therefore relies on the strong and untestable assumption that outcomes after treatment discontinuation were missing at random. On 14 July2015, we conveyed this information to the applicant and request an additional analysis that include all available outcome data from all randomized patients regardless of treatment discontinuation and uses a multiple imputation approach for missing data that more appropriately takes into account treatment adherence.

In the information request response, the applicant pointed out that it was not planned to collect data for patient who were prematurely discontinued. About 9% of patients were prematurely withdrawal in the trial. The applicant proposed several approaches to investigate how the imputation of missing HbA1c data will be affected by treatment adherence. One approach is that missing values were imputed under assumption of monotone missing pattern and then were subtracted by a penalty. The penalty is the treatment dependent least square mean change from baseline to week 24 based on the primary sensitivity analysis on FAS (OC-IR). An alternative approach proposed by the applicant is to implement multiple delta adjustment via multiple imputation, which apply a penalty at each visit. The rationale behind this approach is that patients typically achieve maximum efficacy by week 18 and patient who discontinued at week 6 or 12 are excessively penalized by using single penalty adjustment. The applicant argued that the results were found to be consistent with and supported the primary analysis results detailed in the application (see appendix). The results from the sponsor's two sensitivity analyses were similar to each other. Estimated treatment differences involving the empagliflozin 12.5 mg bid+ metformin 500mg bid arm were notably less favorable for that arm and the estimated treatment differences of the relevant combination arms were notably less favorable when compared with the empagliflozin 5 mg bid alone arm.

As the missingness appears to be related to discontinuation of protocol therapy, I conducted a multiple imputation analysis which assumed any potential treatment effect for those subjects who have missing data will return to the baseline distribution. Specifically, missing data at week 24 was imputed based on a distribution centered at baseline HbA1c value, and with a subject-level prediction standard deviation equal to that from an ANCOVA model performed on observed cases at week 24. The results of this analysis were fairly similar to the results from the sponsor's sensitivity analyses. I believe that the results of the sensitivity analyses may better reflect the true treatment difference than the primary analysis.

The sponsor did not provide justification for the non-inferiority margins for the non-inferiority comparisons. These comparisons were secondary analyses and non-inferiority was not achieved based on the sponsor's selected margin.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Empagliflozin is orally administrated, potent, and selective SGLT-2 inhibitor developed by Boehringer Ingelheim, which reviewed and approved for treatment levels of 10mg and 25 mg.

Empagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2.1.2 History of Drug Development

The clinical development of empagliflozin to improve glycemic control in adults with T2DM started in January 2007. The clinical program established the initial application of empagliflozin as monotherapy, which comprised 30 Phase I trials, 5 Phase II trials, and 13 Phase IIb/III trials. Empagliflozin (Jardiance) was approved by FDA on August 1, 2014. The applicant submitted efficacy supplement package to look for an approval of the revised labelling empagliflozin labelling claim on May 20, 2015.

2.2 Data Source

The data and final study reports were submitted electronically as an eCTD submission. The submission, organized as an .enx file, is archived at the following link:
\\CDSESUB1\evsprod\NDA204629\204629.enx
The information needed for this review was obtained from Module 1 FDA regional information, Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Reports.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

All required documents necessary for conducting a statistical review were submitted. The datasets for the trial 1276.1 were found to be in good organization and were provided as .xpt files. The analysis datasets included both derived and enriched data (such as formatted variables, derived endpoint, etc). I was able to re-produce the results on the primary endpoints and secondary endpoints presented in the Clinical Study Report.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 1276.1 was a phase III randomized, multi-nation, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug naïve patients with type 2 diabetes mellitus.

The main objective of the study was to investigate the efficacy, safety, and tolerability of the combination use of twice daily oral administration empagliflozin (12.5mg or 5 mg bid) and metformin immediate release (1000 mg bid or 500 mg bid) compared with the individual components (empagliflozin 25mg qd, empagliflozin 10mg qd, metformin 1000 mg bid, metformin 500 mg). The additional objective of the trial was to investigate the non-inferiority and subsequent superiority of empagliflozin 25mg qd and empagliflozin 10mg qd vs metformin 1000 mg bid.

Primary and secondary endpoints

The efficacy primary endpoint was the change of HbA1c from baseline after 24 weeks of treatment. The key secondary endpoints were the change of fasting plasma glucose (FPG) from baseline at week 24 and the change of body weight from baseline at week 24.

3.2.2 Statistical Methodologies

Analysis Population

As per the applicant's analysis plan, the full analysis set was the primary analysis population, all randomized patients treated with at least 1 dose of trial medication, with a baseline and at least 1 on-treatment HbA1c assessment and included. All analyses used the planned randomized treatment. However, we noticed that the applicant utilized the datasets that only included those on-treatment patients, which named as FAS (OC) dataset.

Primary and secondary analyses

The applicant performed mixed model repeated measures (MMRM) model to assess the efficacy of empagliflozin+metformin compared with metformin or empagliflozin. The model included baseline endpoint as covariate, baseline renal function, region treatment, visit, and visit-treatment interaction. Unstructured covariance was used in the model. If unstructured covariance fails to converge, the following structures will be used: compound symmetry, variance components and Toeplits.

Testing strategy for adjusting multiplicity

The applicant proposed a hierarchical testing sequence for superiority of the combination therapy over monotherapy (see in Figure 1). If the testing sequence for superiority was established as proposed in Figure 1, then two non-inferiority tests will be conducted also in a hierarchical order as in Figure 2.

FDA approach for handling missing data

As the applicant did not continue to collect data for patients once they had prematurely withdrawn from treatment and the fact that a majority of patients who have missing data at week 24 discontinued treatment., an FDA's sensitivity analysis to address missing data used a different imputation strategy by assuming that patients who discontinued study therapy would no longer benefit from the study medication and will be "washed out." Missing data at week 24 was imputed using multiple imputation where the distribution was centered at baseline HbA1c value. The variance for the distribution used the subject-level prediction standard deviation based on ANCOVA model performed on observed cases at week 24.

In this review, the sensitivity analyses conducted by the FDA were performed on the treated set, which included all randomized subjects who at least took 1 dose of study medication regardless of treatment adherence. As the study was a double-blind randomized study, the integrity of randomization is still maintained when the analyses are performed on the treated set (TS)..

Figure 1 Hierarchical testing sequence for superiority of the combination therapy over monotherapy

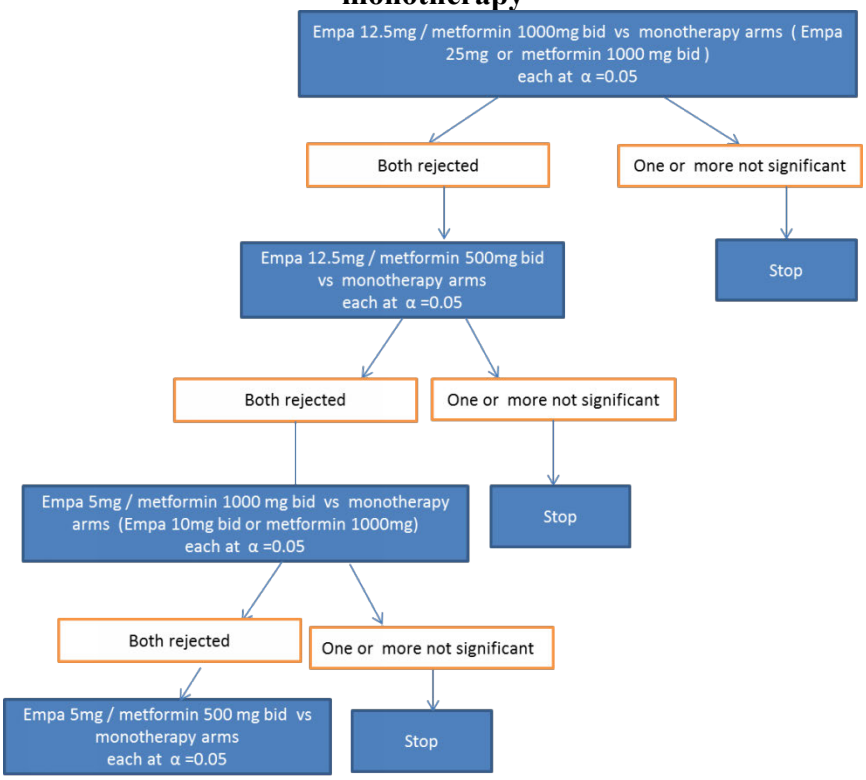
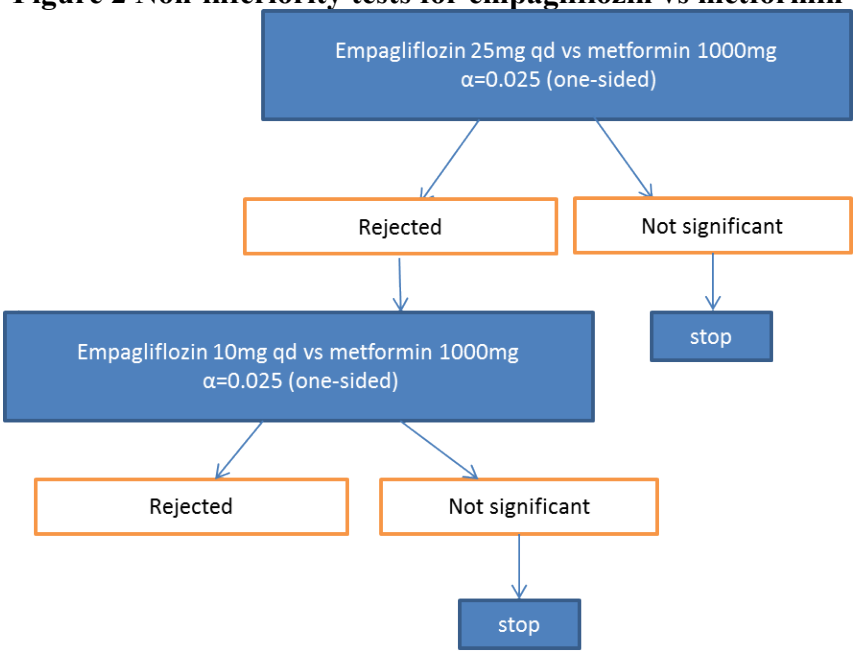


Figure 2 Non-inferiority tests for empagliflozin vs metformin



3.2.3 Patient Disposition, Demographic and Baseline Characteristics

According to the applicant's protocol, the randomized set (RS) included all randomized patients to one of the study arms, regardless of whether any trial medications were taken. The defined full analysis set (FAS) comprised all randomized patients treated with at least 1 dose of trial medication, with a baseline and at least 1 on-treatment HbA1c assessment.

Table 1 presented the patient disposition of the study for the treated set. 1364 patients were randomized to one of the study arms, and 4 patients did not treated with the study medication. Of 1360 patients, 1230 (90.8%) patients completed treatment period, 37 (2.7%) patients refused to continue taking the study medication, 27 (2%) patients were withdrawal due to subject request, 11 (0.8%) patients violated protocol, and other reasons were detailed in Table 1.
Table 2 summarized the demographics and baseline characteristics of patients in the study 1276.1. Across the treatment groups, 18% to 19.4% were patients enrolled from North America. The average age of patients across the treatments ranged from 51 to 52 years old. There were no striking imbalances between the treatment arms in the important baseline characteristics in the study.

Table 3 summarized the percentage of missingness in the study, where the overall missing rate at week 24 was 10.2%. Across the treatment groups, the missing rate ranged from 6.5% to 12.3% (see Table 4).

Table 1 Patient Disposition for Treated Set

Disposition Reasons	E10 QD	E12.5+M1000 BID	E12.5 +M500 BID	E25 QD	E5+M1000 BID	E5+M500 BID	M1000 BID	M500 BID	Total
Patient completed treatment period	160	161	153	150	154	156	150	151	1235
Lack of efficacy	0	0	0	0	0	0	1	0	1
Non-compliant with protocol	1	1	1	2	0	1	2	3	11
Patient refusal to continue taking trial medication	3	2	5	4	4	4	8	7	37
Unexpected worsening of disease under study	0	0	0	0	0	0	1	0	1
Unexpected worsening of other pre-existing disease/condition	0	0	0	1	0	0	1	0	2
Withdrawal by subject	4	0	6	3	7	2	3	2	27
Other	1	0	0	4	2	3	0	3	13
Other adverse event	3	6	5	3	4	3	4	5	33
Total treated subjects	172	170	170	167	171	169	170	171	1360

Note: BID- twice daily; QD- once daily; E- empagliflozin ; M- metformin ;

Table 2 Demographic and Baseline Characteristics-Randomized Set

	E10 qd (n=172)	E12.5+M1000 bid (n=170)	E12.5+M500 bid (n=170)	E25 qd (n=168)	E5+M1000 bid (n=172)	E5+ M500 bid (n=170)	M1000 bid (n=171)	M500 bid (n=171)
Region								
Asia	37 (21.5%)	37 (21.8%)	39 (22.9%)	33 (19.6%)	39 (22.7%)	37 (21.8%)	33 (19.3%)	40 (23.4%)
Europe	42 (24.4%)	41 (24.1%)	43 (25.3%)	46 (27.4%)	38 (22.1%)	50 (29.4%)	48 (28.1%)	43 (25.1%)
Latin America	48 (27.9%)	47 (27.6%)	47 (27.6%)	48 (28.6%)	48 (27.9%)	47 (27.6%)	47 (27.5%)	47 (27.5%)
North America	31 (18.0%)	33 (19.4%)	33 (19.4%)	31 (18.5%)	33 (19.2%)	32 (18.8%)	33 (19.3%)	32 (18.7%)
Other	14 (8.14%)	12 (7.06%)	8 (4.71%)	10 (5.95%)	14 (8.14%)	4 (2.35%)	10 (5.85%)	9 (5.26%)
Sex								
Female	72 (41.9%)	81 (47.6%)	61 (35.9%)	83 (49.4%)	71 (41.3%)	67 (39.4%)	76 (44.4%)	83 (48.5%)
Male	100 (58.1%)	89 (52.4%)	109 (64.1%)	85 (50.6%)	101 (58.7%)	103 (60.6%)	95 (55.6%)	88 (51.5%)
Age								
Mean (SD)	53 (10.6)	54 (10.7)	51 (10.6)	53 (10.9)	53 (11.3)	52 (11.6)	52 (10.9)	53 (10.8)
<65	149 (86.6%)	144 (84.7%)	152 (89.4%)	144 (85.7%)	142 (82.6%)	146 (85.9%)	149 (87.1%)	146 (85.4%)
>=65	23 (13.4%)	26 (15.3%)	18 (10.6%)	24 (14.3%)	30 (17.4%)	24 (14.1%)	22 (12.9%)	25 (14.6%)
Race								
ASIAN	63 (36.6%)	69 (40.6%)	71 (41.8%)	60 (35.7%)	68 (39.5%)	68 (40.0%)	67 (39.2%)	66 (38.6%)
BLACK	7 (4.07%)	7 (4.12%)	9 (5.29%)	8 (4.76%)	8 (4.65%)	7 (4.12%)	7 (4.09%)	10 (5.85%)
WHITE	102 (59.3%)	94 (55.3%)	90 (52.9%)	100 (59.5%)	96 (55.8%)	95 (55.9%)	97 (56.7%)	95 (55.6%)

	E10 qd (n=172)	E12.5+M1000 bid (n=170)	E12.5+M500 bid (n=170)	E25 qd (n=168)	E5+M1000 bid (n=172)	E5+ M500 bid (n=170)	M1000 bid (n=171)	M500 bid (n=171)
Time since Diagnosis of T2DM								
<= 1 YEAR	82 (47.7%)	100 (58.5%)	19 (35.8%)	91 (53.5%)	92 (54.8%)	103 (59.9%)	101 (59.4%)	91 (53.2%)
<= 10 YRS BUT > 5 YR	18 (10.5%)	16 (9.36%)	8 (15.1%)	21 (12.4%)	22 (13.1%)	20 (11.6%)	16 (9.41%)	18 (10.5%)
<= 5 YRS BUT > 1 YR	62 (36.0%)	45 (26.3%)	20 (37.7%)	45 (26.5%)	50 (29.8%)	40 (23.3%)	50 (29.4%)	51 (29.8%)
> 10 YEARS	10 (5.81%)	10 (5.85%)	6 (11.3%)	13 (7.65%)	4 (2.38%)	9 (5.23%)	3 (1.76%)	11 (6.43%)
Baseline eGFR								
Mean (SD)	94 (21.4)	92 (19.2)	95 (20.9)	92 (19.8)	93 (22.0)	94 (22.3)	93 (20.1)	91 (19.3)
Baseline FPG								
Mean (SD)	170 (39.0)	167 (40.8)	173 (43.8)	177 (48.7)	163 (41.5)	166 (39.4)	169 (48.4)	172 (38.9)
Baseline HbA1c								
Mean (SD)	9 (1.2)	9 (1.1)	9 (1.3)	9 (1.3)	9 (1.2)	9 (1.2)	9 (1.1)	9 (1.0)
Baseline BMI								
Mean (SD)	30 (5.2)	30 (5.3)	30 (5.1)	31 (5.8)	31 (5.1)	30 (5.3)	30 (6.0)	30 (5.8)
Baseline SBP								
Mean (SD)	128 (14.5)	127 (13.7)	127 (14.7)	128 (15.8)	127 (13.6)	127 (13.2)	129 (15.6)	128 (13.9)
Baseline DBP								
Mean (SD)	79 (9.6)	79 (8.0)	79 (9.2)	79 (9.6)	78 (9.0)	79 (8.6)	79 (9.3)	79 (8.6)

Note: bid- twice daily; qd- once daily; E- empagliflozin ; M- metformin ; 4 subjects were never received study medication

Table 3 Percentage of missingness –Treated Set

	Baseline	week 6	week 12	week 18	week 24
Missing	0	46 (3.4%)	87 (6.4%)	112 (8.2 %)	138 (10.2%)
Non-missing	1360	1314 (96.6%)	1273 (93.6%)	1248 (91.7%)	1222 (89.8%)

Table 4 Percentage of missingness by treatment group –Treated Set

Planned Treatment	n	Baseline	Week 6	Week 12	Week 18	Week 24
E10 QD	172	0.0%	2.9%	2.9%	5.8%	7.6%
E12.5+M1000 BID	170	0.0%	1.2%	4.7%	5.9%	6.5%
E12.5+M500 BID	170	0.0%	3.5%	8.2%	9.4%	11.8%
E25 QD	167	0.0%	3.6%	6.0%	10.8%	12.0%
E5+M1000BID	171	0.0%	2.9%	5.8%	7.0%	11.1%
E5+M500 BID	169	0.0%	5.9%	5.9%	7.7%	8.9%
M1000 BID	170	0.0%	4.7%	10.0%	10.0%	11.2%
M500 BID	171	0.0%	2.3%	7.6%	9.4%	12.3%

3.2.4 Results and Conclusions

3.2.4.1 Primary Endpoint

Table 5 summarized the results on HbA1c (%) change from baseline at week 24 based on approach assuming that patients return to baseline distribution if patients discontinued the therapy at the primary endpoint. According to the proposed hierarchical testing, the superiority of combination therapy over monotherapy was all achieved at significant level of 0.05. However, the non-inferiority of empagliflozin 25 mg against metformin 1000 mg and the non-inferiority of empagliflozin 10 mg against metformin 1000 mg were not significant where the specified non-inferiority margin was 0.35%. Empagliflozin alone appears inferior to metformin alone in reducing HbA1c among patients with type 2 diabetes.

Table 6 presented the results on HbA1c (%) change from baseline at week 24 that provided by sponsor using MMRM approach, which assumes that the behavior of missing data were the same as that of observed data. The sponsor utilized the dataset of the subjects who were only on-treatment to perform the analysis. However, the approach did not evaluate an intention-to-treat estimand, i.e., the difference in HbA1c change in all randomized patients regardless of treatment adherence to treatment or use of rescue, even though the statistical decisions did not change based on the applicant's results.

Table 7compared the analysis results of Table 5 and Table 6. The overall test findings were similar between two different approaches, which concluded that the combination uses of empagliflozin and metformin were superior to empagliflozin or metformin alone. However, the sponsor's approach relied on a strong assumption about the missing data and did not take account of wash out effect when patients were no longer on study medication. The estimated treatment effects of difference in Table 6 were larger than in Table 5.

Table 5 HbA1c (%) change from baseline ANOVA results at Week 24 –TS (OC-IR) (FDA's Results)

	LS Mean (SE)	Comparison vs E25 QD (95% CI) P-value	Comparison vs M1000 BID (95% CI) P-value	Comparison vs M500 BID (95% CI) P-value	Comparison vs E10 QD (95% CI) P-value
Combination					
E12.5+M1000 BID (n=170)	-1.77 (0.14)	-0.79 (-1.04, -0.54) <0.0001	-0.38 (-0.63, -0.13) <0.0001		
E12.5+M500 BID (n=170)	-1.44 (0.14)	-0.45 (-0.71, -0.20) 0.0004		-0.54 (-0.79, -0.29) <0.0001	
E5+M1000 BID (n=171)	-1.69 (0.14)		-0.30 (-0.55, -0.05) 0.0203		-0.63 (-0.88, -0.38) <0.0001
E5+M500 BID (n=169)	-1.60 (0.14)			-0.70 (-0.95, -0.45) <0.0001	-0.53 (-0.78, -0.29) <0.0001

	LS Mean (SE)	Comparison vs M1000 BID (95% CI) P-value*
Monotherapy		
E25 QD (n=167)	-0.99 (0.14)	0.41 (0.16, 0.66) 0.6471
E10 QD (n=172)	-1.06 (0.14)	0.33 (0.08,0.58) 0.8910
M1000 BID (n=170)	-1.40 (0.14)	
M500 BID (n=171)	-0.90 (0.14)	

Note: Model includes baseline HbA1c as linear covariate and baseline eGFR, region, treatment as fixed effects. Missing data are imputed using multiple imputation and all observed cases of change from baseline at week 24 weeks are treated as non-missing.
*non-inferiority test at alpha=0.025 with the specified margin of 0.35%

Table 6 HbA1c (%) change from baseline MMRM results at week 24 – FAS (OC) (Sponsor's Report)

	E12.5+M1000 bid	E12.5+M500 bid	E5+M1000 bid	E5+M500 bid	E25 qd	E10 qd	M1000 bid	M500 bid
Number of patients in analysis set	169	165	167	161	164	169	164	168
Baseline								
Mean baseline HbA_{1c} (SE)	8.66 (0.09)	8.84 (0.10)	8.65 (0.10)	8.68 (0.10)	8.86 (0.10)	8.62 (0.10)	8.55 (0.09)	8.69 (0.08)
Week 24								
Number of analysed patients	159	149	151	153	143	156	146	142
Mean HbA_{1c} (SE)	6.56 (0.08)	6.84 (0.09)	6.49 (0.08)	6.67 (0.07)	7.30 (0.09)	7.18 (0.09)	6.72 (0.08)	7.35 (0.11)
Change from baseline								
Mean (SE)	-2.12 (0.09)	-1.99 (0.11)	-2.12 (0.09)	-2.01 (0.09)	-1.48 (0.10)	-1.35 (0.09)	-1.81 (0.10)	-1.30 (0.09)
Adjusted[1] mean (SE)	-2.08 (0.08)	-1.93 (0.08)	-2.07 (0.08)	-1.98 (0.08)	-1.36 (0.08)	-1.35 (0.08)	-1.75 (0.09)	-1.18 (0.08)
Comparison vs. M1000 bid								
Adjusted[1] mean (SE)	-0.33 (0.12)	-	-0.33 (0.12)	-	0.39 (0.12)	0.40 (0.12)	-	-
95% CI	(-0.56, -0.10)	-	(-0.56, -0.09)	-	(0.15, 0.62)	(0.16, 0.63)	-	-
p-value non- inferiority[2]					0.6246	0.6558		
p-value superiority	0.0056	-	0.0062	-	-	-	-	-
Comparison vs. E25 qd								
Adjusted[1] mean (SE)	-0.72 (0.12)	-0.57 (0.12)	-	-	-	-	-	-
95% CI	(-0.95, -0.48)	(-0.81, -0.34)	-	-	-	-	-	-
p-value superiority	<0.0001	<0.0001	-	-	-	-	-	-
Comparison vs. M500 bid								
Adjusted[1] mean (SE)	-	-0.75 (0.12)	-	-0.79 (0.12)	-	-	-	-
95% CI	-	(-0.98, -0.51)	-	(-1.03, -0.56)	-	-	-	-
p-value superiority	-	<0.0001	-	<0.0001	-	-	-	-
Comparison vs. E10 qd								
Adjusted[1] mean (SE)	-	-	-0.72 (0.12)	-0.63 (0.12)	-	-	-	-
95% CI	-	-	(-0.95, -0.49)	(-0.86, -0.40)	-	-	-	-
p-value superiority	-	-	<0.0001	<0.0001	-	-	-	-

SE = standard error; CI = confidence interval

[1] The MMRM model includes baseline HbA_{1c} as linear covariate and baseline eGFR (MDRD), geographical region, treatment, visit, and visit-by-treatment interaction as fixed effects. The covariance used to fit the model was unstructured.

[2] One-sided test relative to a pre-specified margin of 0.35%

Table 7 Summary of results based on FDA and Sponsor's approach (for only comparisons which the sponsor wants in the product label)

	JARDIANCE 25 mg + Metformin 1000 mg N=170	JARDIANCE 25 mg + Metformin 2000 mg N=170	JARDIANCE 25 mg N=167	JARDIANCE 10 mg + Metformin 1000 mg N=169	JARDIANCE 10 mg + Metformin 2000 mg N=171	JARDIANCE 10 mg N=172	Metformin 1000 mg N=171	Metformin 2000 mg N=170
FDA analysis results								
Change from baseline (adjusted mean)	-1.44	-1.77	-0.99	-1.60	-1.69	-1.06	-0.90	-1.40
Comparison vs JARDIANCE (adjusted mean) (95% CI)	-0.45 (-0.71, -0.20)	-0.79 (-1.04, -0.54)	--	-0.53 (-0.78, -0.29)	-0.63 (-0.88, -0.38)		--	--
Comparison vs metformin (adjusted mean) (95% CI)	-0.54 (-0.79, -0.29)	-0.38 (-0.63, -0.13)	--	-0.70 (-0.95, -0.45)	-0.30 (-0.55, -0.05)		--	--
Applicant analysis results								
Change from baseline (adjusted mean)	-1.93	-2.08	-1.36	-1.98	-2.07	-1.35	-1.18	-1.75
Comparison vs JARDIANCE (adjusted mean) (95% CI)	-0.57 (-0.81, -0.34)	-0.72 (-0.95, -0.48)	--	-0.63 (-0.86, -0.40)	-0.72 (-0.95, -0.49)		--	--
Comparison vs metformin (adjusted mean) (95% CI)	-0.75 (-0.98, -0.51)	-0.33 (-0.56, -0.10)	--	-0.79 (-1.03, -0.56)	-0.33 (-0.56, -0.09)		--	--

The applicant proposed several approaches to investigate how the imputation of missing HbA1c data will be affected by treatment adherence. One approach is that missing values were imputed under assumption of monotone missing pattern and then were subtracted by a penalty. The penalty is the treatment dependent least square mean change from baseline to week 24 based on the primary sensitivity analysis on FAS (OC-IR). An alternative approach proposed by the applicant is to implement multiple delta adjustment via multiple imputation, which apply a penalty at each visit. The rationale behind this approach is that patients typically achieve maximum efficacy by week 18 and patient who discontinued at week 6 or 12 are excessively penalized by using single penalty adjustment. The applicant argued that the results were found to be consistent with and supported the primary analysis results detailed in the application (see appendix). The results from the sponsor's two sensitivity analyses were similar to each other. Estimated treatment differences involving the empagliflozin 12.5 mg bid+ metformin 500mg bid arm were notably less favorable for that arm and the estimated treatment differences of the relevant combination arms were notably less favorable when compared with the empagliflozin 5 mg bid alone arm.

The results of the sponsor's sensitivity analyses were fairly similar to the results from the FDA sensitivity analysis.

3.2.4.2 Secondary Endpoints

According to the applicant's statistical protocol, the secondary endpoints will be analyzed if all hierarchical tests for the primary endpoint are successful. However, the prespecified non-inferiority test of comparing empagliflozin to metformin failed. Therefore, the analyses for secondary endpoints were not conducted.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section included the analysis results of the primary endpoint performed within subgroup levels for the study. Table 8 summarized the subgroup factors and levels for subgroup analyses. All subgroup analyses on primary endpoints were performed using an ANCOVA model in the ITT population with treatment, baseline HbA1c, region, baseline renal function and interaction of subgroup variable and treatment.

Table 8 Lists of Subgroup Analyses Performed in Study 1276.1

Factor	Levels
Region	North America; Latin America; Europe; Asia; Other
Age	<65 years; ≥ 65 years
Race	White; Black; Asian; Other
Ethnicity	Hispanic or Latino; Not Hispanic or Latino
Sex	Female; Male
Baseline renal function	<60 (moderate/severe) ; 60 to < 90 (mild) ; >=90 (normal)

Due to complexity of the number of treatment groups and repeatability of treatment comparisons, the subgroup analyses were performed through each primary analysis component separately (e.g combination products vs two monotherapy). Table 9 presented results of the formal tests for the

interaction of subgroup and separate component. The interaction of baseline renal function and treatment groups (E12.5+M500, E12.5, and M500) was significant, yet very limited patients with severe renal function (<60) were enrolled in the study. We acknowledge that the study was not powered for subgroup analyses and all findings are considered as exploratory. Figure 3 to Figure 10 summarized the estimates and stand error with 95% confidence interval for each examined subgroup variables. All findings were relatively consistent across levels of the subgroups.

Table 9 Summary of p-value for overall interaction test of subgroup and specified treatment groups

	E12.5+M1000BID, E12.5 QD, M10000 BID	**E12.5+M500BID, E12.5QD, M500 BID**	**E5+M1000 BID, E5 QD, M1000 BID**	**E5+M500BID, E5 QD, M500 BID**
Region	0.4281	0.0990	0.6026	0.1309
Age	0.6374	0.1666	0.8587	0.3505
Race	0.4226	0.2230	0.0748	0.4357
Ethnicity	0.3534	0.3836	0.8108	0.3527
Sex	0.8713	0.3204	0.0473*	0.0548
Baseline renal function	0.3197	0.0325*	0.1417	0.2339

*indicates where p-value<0.05

Figure 3 Forest plot for subgroup analysis of E12.5 +M1000 vs M1000

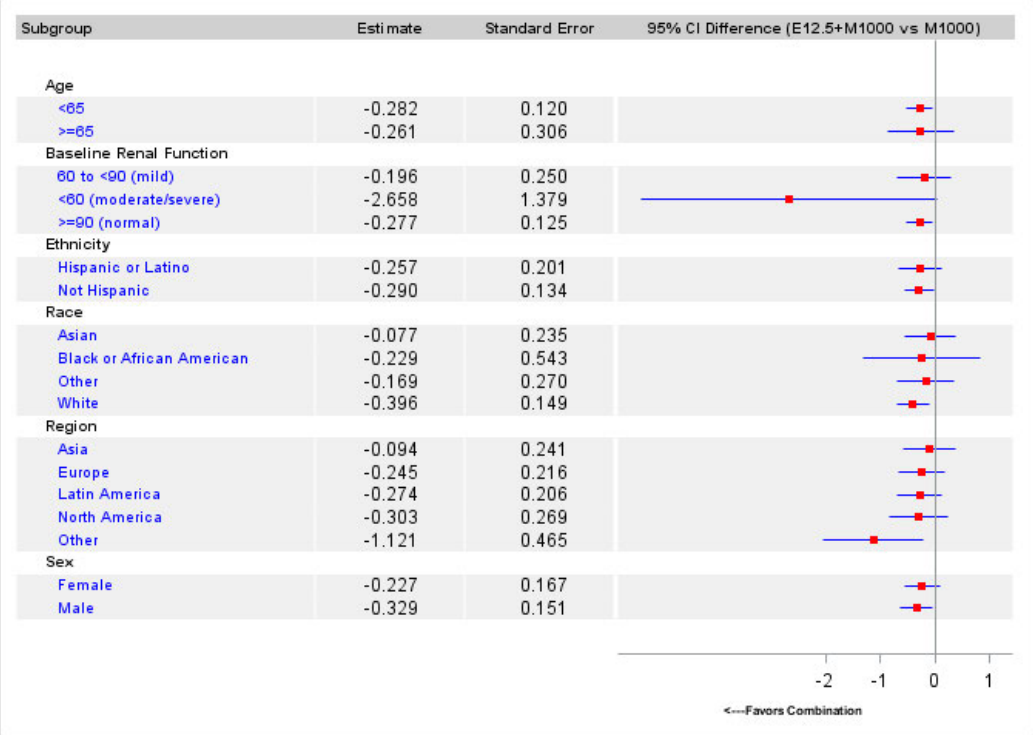


Figure 4 Forest plot for subgroup analysis of E12.5+M1000 vs E25

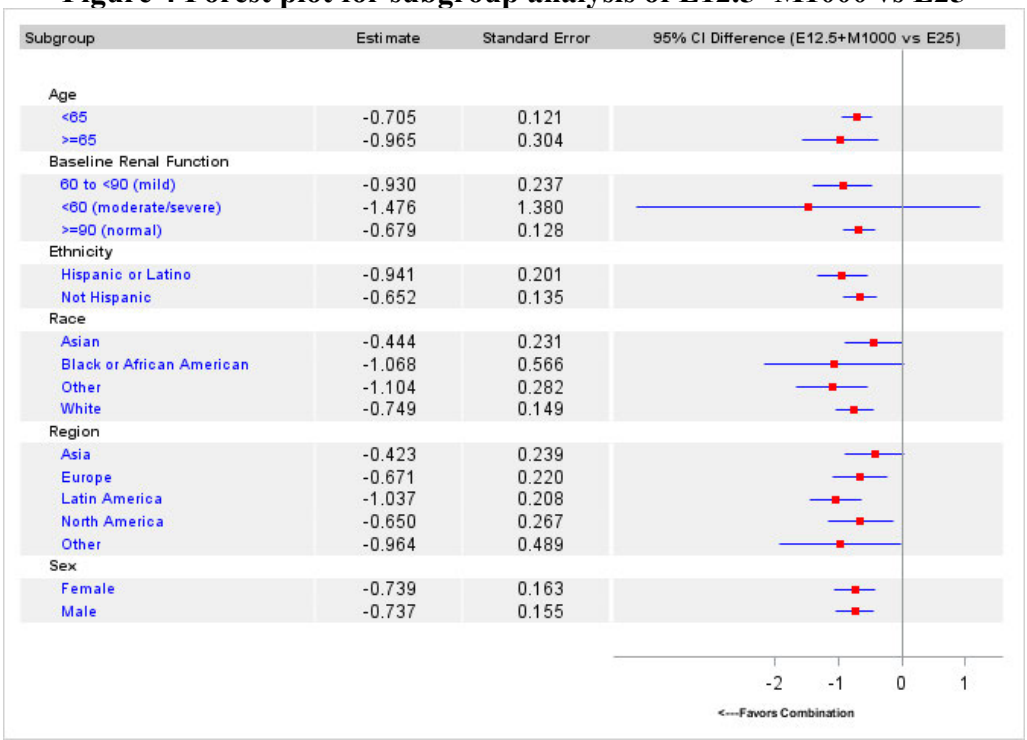


Figure 5 Forest plot for subgroup analysis of E12.5+M500 vs M500

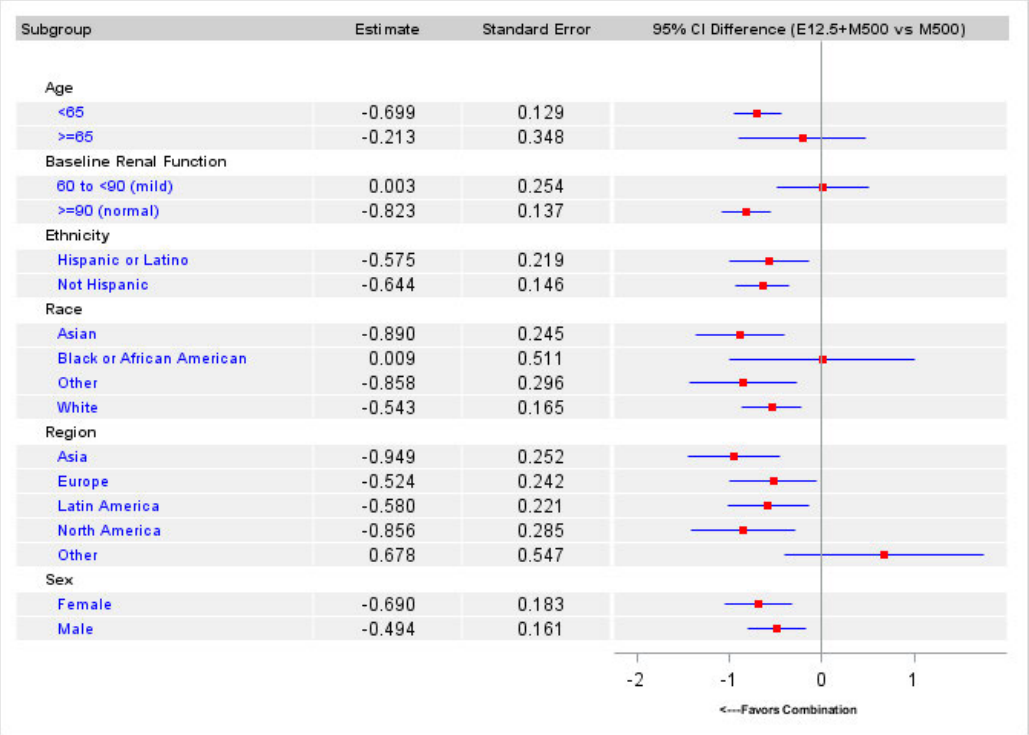


Figure 6 Forest plot for subgroup analysis of E12.5+M500 vs E25

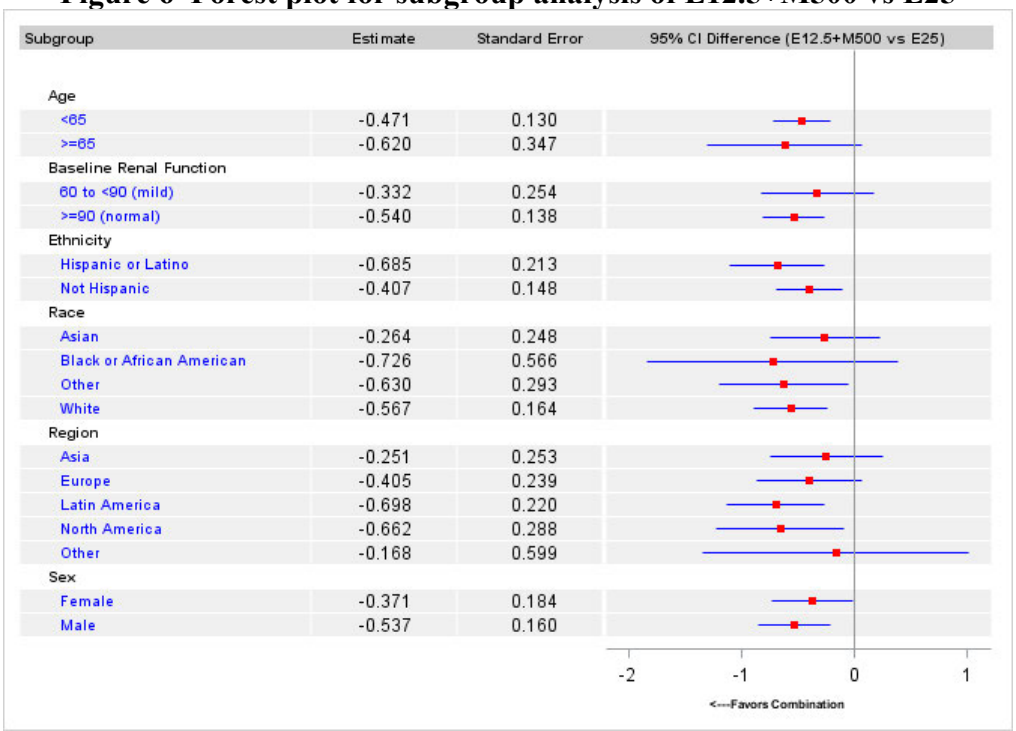


Figure 7 Forest plot for subgroup analysis of E5+M1000 vs M1000

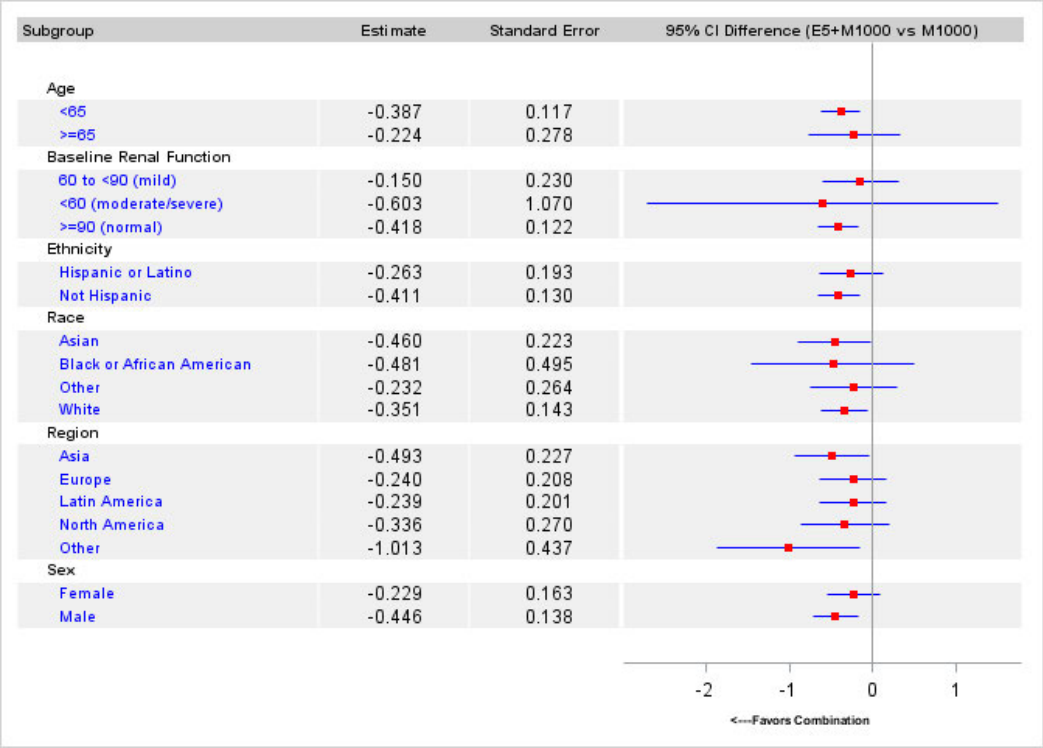


Figure 8 Forest plot for subgroup analysis of E5+M1000 vs E10

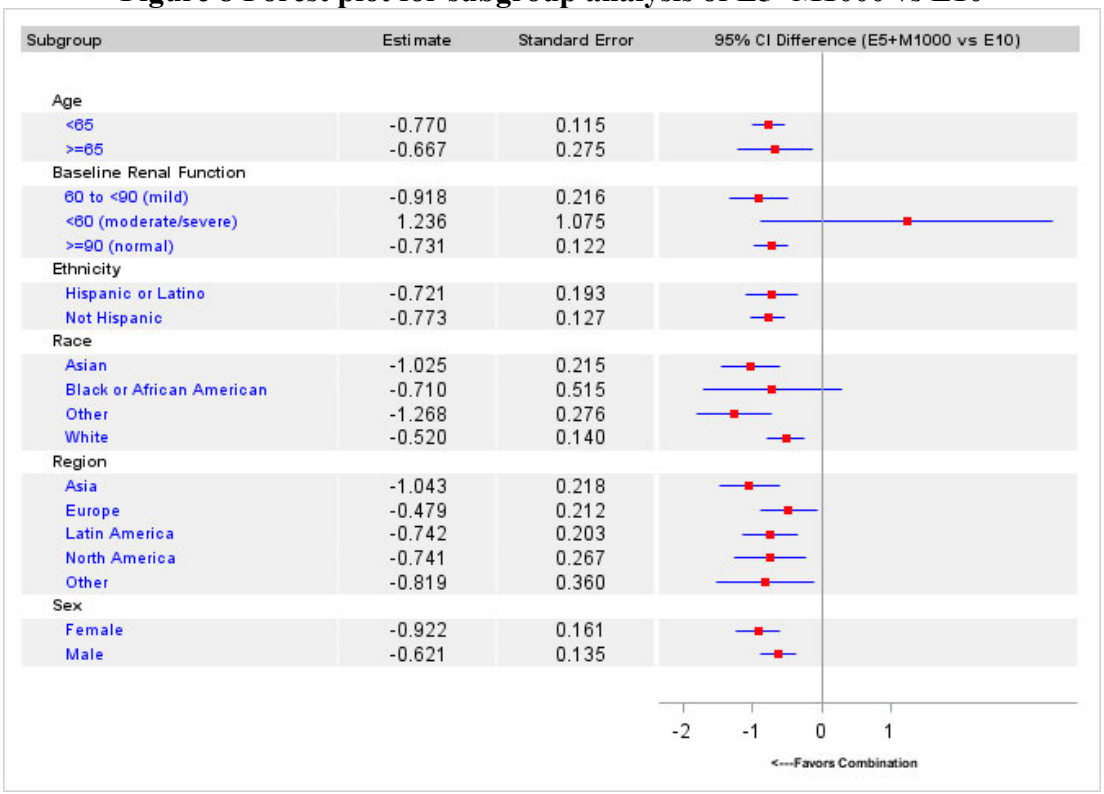


Figure 9 Forest plot for subgroup analysis of E5+M500 vs M500

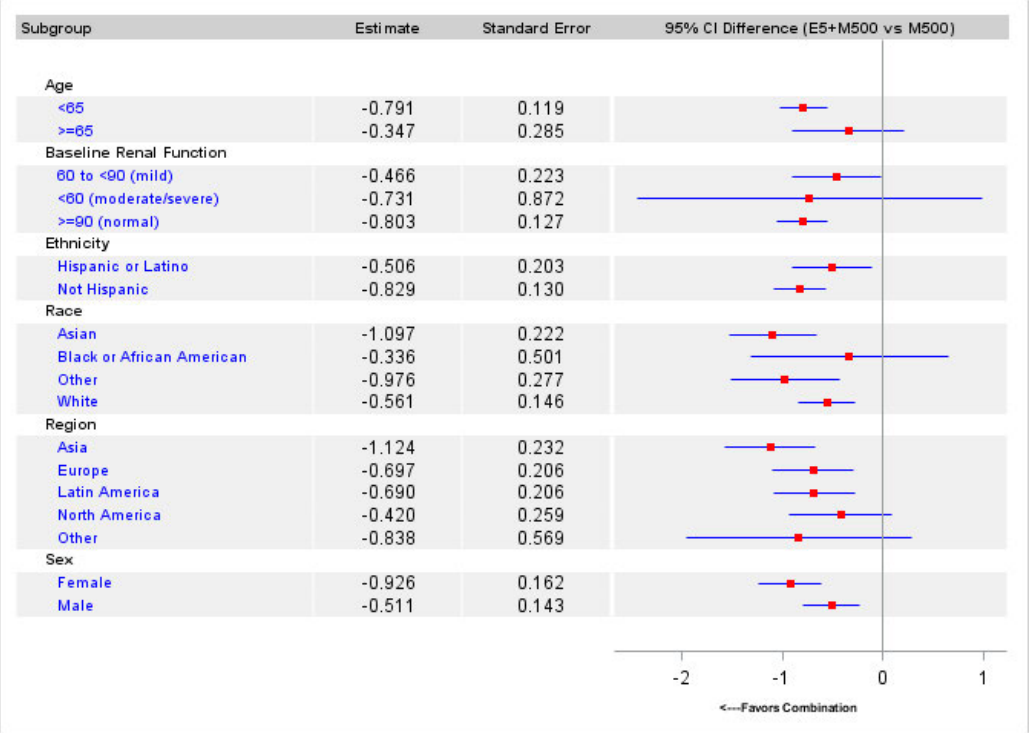
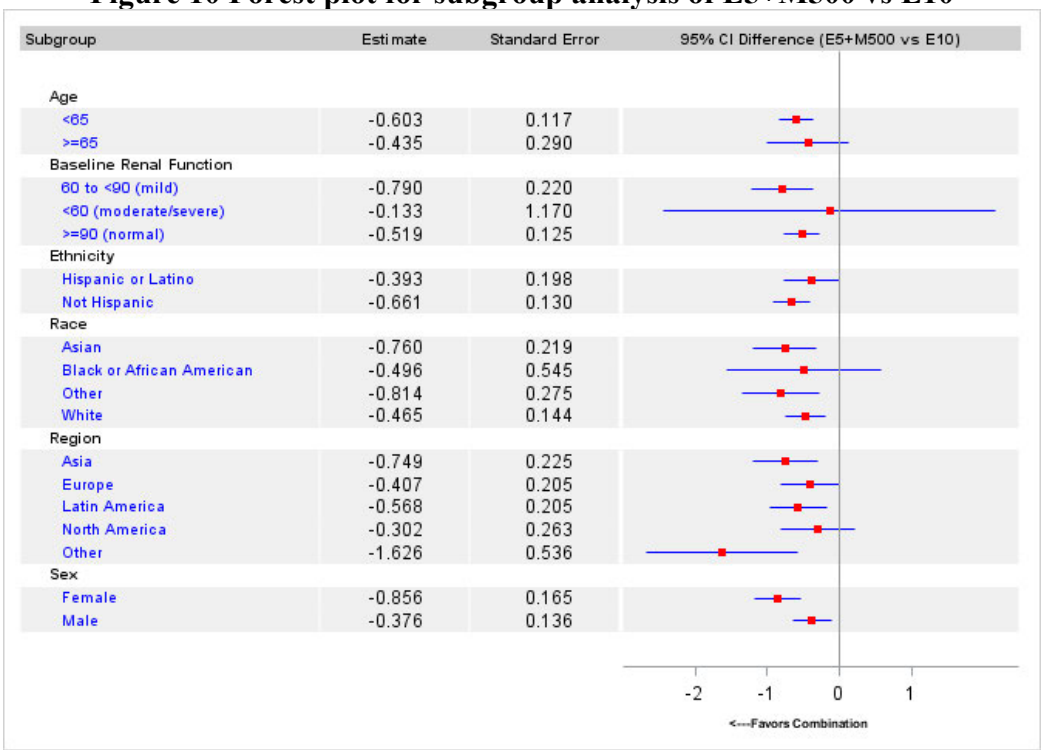


Figure 10 Forest plot for subgroup analysis of E5+M500 vs E10



5 SUMMARY AND CONCLUSIONS

5.1 Summary and Conclusions

The FDA analysis results were found to be consistent with applicant's primary analysis. The combination uses of empagliflozin (12.5mg or 5 mg) and metformin (1000 mg or 500mg) showed statistically significance comparing with empagliflozin (25mg or 10 mg) or metformin (1000mg or 500 mg) alone. However, empagliflozin (25mg or 10 mg) failed to demonstrate the non-inferiority comparing with metformin (1000 mg or 500 mg), where the specified the non-inferiority margin was 0.35%.

5.2 Labeling Recommendations

1. (b) (4) My recommendation for the labelling is that the estimate of treatment effect should be based on an ITT estimand, i.e., the difference in week 24 HbA1c in all randomized subjects regardless of adherence to assigned treatment or use of rescue therapy, or similar population that maintains the randomization.

(b) (4)

(b) (4)

6 APPENDIX

Table 10 HbA1c (%) change from baseline ANCOVA results at week 24 − RS (OC−IR). Missing data imputed via multiple imputation. Single delta adjustment in all groups, adjustment value specified in footnotes for each treatment group

Visit Description Statistic	E12.5+M1000B	E12.5+M500B	E5+M1000BID	E5+M500BID	Empa25 QD	Empa10 QD	Met1000 BID	Met500 BID
Number of patients in analysis set	170	170	172	170	168	172	171	171
Number of analysed patients	170	170	172	170	168	172	171	171
Baseline mean (SE)	8.66 (0.09)	8.83 (0.10)	8.67 (0.09)	8.66 (0.10)	8.88 (0.10)	8.62 (0.09)	8.60 (0.09)	8.68 (0.08)
Week 24								
Values at visit								
Mean (SE)	6.70 (0.09)	7.06 (0.10)	6.78 (0.10)	6.87 (0.08)	7.56 (0.10)	7.35 (0.09)	7.05 (0.11)	7.60 (0.11)
Adjusted* mean (SE)	6.72 (0.09)	7.00 (0.09)	6.80 (0.09)	6.89 (0.09)	7.48 (0.09)	7.38 (0.09)	7.10 (0.09)	7.61 (0.09)
Change from baseline								
Mean (SE)	-1.96 (0.10)	-1.78 (0.11)	-1.88 (0.10)	-1.79 (0.10)	-1.32 (0.11)	-1.28 (0.09)	-1.54 (0.12)	-1.09 (0.09)
Adjusted* mean (SE)	-1.98 (0.09)	-1.70 (0.09)	-1.90 (0.09)	-1.81 (0.09)	-1.22 (0.09)	-1.32 (0.09)	-1.60 (0.09)	-1.09 (0.09)
Comparison vs Met1000 BID								
Adjusted* mean (SE)	-0.38 (0.13)		-0.30 (0.12)					
95.0% CI	(-0.63,-0.14)		(-0.55,-0.06)					
p-value	0.0022		0.0162					
Comparison vs Empa25 QD								
Adjusted* mean (SE)	-0.77 (0.13)	-0.49 (0.13)						
95.0% CI	(-1.01,-0.52)	(-0.73,-0.24)						
p-value	<0.0001	0.0001						
Comparison vs Met500 BID								
Adjusted* mean (SE)		-0.61 (0.13)		-0.72 (0.13)				
95.0% CI		(-0.86,-0.36)		(-0.97,-0.47)				
p-value		<0.0001		<0.0001				
Comparison vs Empa10 QD								
Adjusted* mean (SE)			-0.58 (0.12)	-0.49 (0.13)				
95.0% CI			(-0.83,-0.34)	(-0.74,-0.25)				
p-value			<0.0001	<0.0001				

* Model includes baseline HbA1c as linear covariate(s) and baseline eGFR (MDRD), geographical region, treatment as fixed effect(s).

Note: Adjustments are E12.5+M1000B=2.09, E12.5+M500B=1.93, E5+M1000BID=2.10, E5+M500BID=1.97, Empa25 QD=1.41, Empa10 QD=1.39, Met1000 BID=1.75, Met500 BID=1.23.

Table 11 HbA1c (%) change from baseline ANCOVA results at week 24 − RS (OC−IR). Missing data imputed via multiple imputation. Multiple delta adjustment in all groups, adjustment value taken from adj. mean in MMRM

Visit Description Statistic	E12.5+M1000B	E12.5+M500B	E5+M1000BID	E5+M500BID	Empa25 QD	Empa10 QD	Met1000 BID	Met500 BID
Number of patients in analysis set	170	170	172	170	168	172	171	171
Number of analysed patients	170	170	172	170	168	172	171	171
Baseline mean (SE)	8.66 (0.09)	8.83 (0.10)	8.67 (0.09)	8.66 (0.10)	8.88 (0.10)	8.62 (0.09)	8.60 (0.09)	8.68 (0.08)
Week 24								
Values at visit								
Mean (SE)	6.70 (0.08)	7.06 (0.10)	6.78 (0.10)	6.87 (0.08)	7.55 (0.10)	7.35 (0.09)	7.05 (0.11)	7.60 (0.11)
Adjusted* mean (SE)	6.71 (0.09)	7.00 (0.09)	6.80 (0.09)	6.89 (0.09)	7.48 (0.09)	7.38 (0.09)	7.09 (0.09)	7.61 (0.09)
Change from baseline								
Mean (SE)	-1.96 (0.10)	-1.77 (0.11)	-1.88 (0.10)	-1.79 (0.10)	-1.32 (0.11)	-1.28 (0.09)	-1.55 (0.12)	-1.09 (0.09)
Adjusted* mean (SE)	-1.99 (0.09)	-1.70 (0.09)	-1.90 (0.09)	-1.81 (0.09)	-1.22 (0.09)	-1.32 (0.09)	-1.61 (0.09)	-1.09 (0.09)
Comparison vs Met1000 BID								
Adjusted* mean (SE)	-0.38 (0.13)		-0.30 (0.13)					
95.0% CI	(-0.63,-0.13)		(-0.54,-0.05)					
p-value	0.0024		0.0182					
Comparison vs Empa25 QD								
Adjusted* mean (SE)	-0.77 (0.13)	-0.48 (0.13)						
95.0% CI	(-1.01,-0.52)	(-0.73,-0.23)						
p-value	<0.0001	0.0001						
Comparison vs Met500 BID								
Adjusted* mean (SE)		-0.61 (0.13)		-0.72 (0.13)				
95.0% CI		(-0.86,-0.36)		(-0.97,-0.48)				
p-value		<0.0001		<0.0001				
Comparison vs Empa10 QD								
Adjusted* mean (SE)			-0.58 (0.12)	-0.49 (0.12)				
95.0% CI			(-0.82,-0.34)	(-0.74,-0.25)				
p-value			<0.0001	<0.0001				

* Model includes baseline HbA1c as linear covariate(s) and baseline eGFR (MDRD), geographical region, treatment as fixed effect(s).

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/s/

SHUXIAN Z SINKS
02/12/2016

MARK D ROTHMANN
02/12/2016
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY MEMORANDUM

NDA	NDA 204629/S-005 (SE-8)
Submission Date	July 10, 2015
Brand Name	Jardiance
Generic Name	Empagliflozin
Reviewer	Suryanarayana Sista, Ph.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Boehringer Ingelheim
Formulation; Strength	Tablets: 10 mg; 25 mg
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Background

NDA 204629 (empagliflozin) was approved on August 1, 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The product is being marketed under the trade name, Jardiance. The sponsor, Boehringer Ingelheim, conducted a Phase 3 study entitled **"24-week randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug naive patients with type 2 diabetes mellitus (Study 1276.1)".**

The sponsor is proposing to amend the Jardiance label with data from completed clinical study. In addition, changes to the label addressing the risks of ketoacidosis and urosepsis with the use of SGLT-2 inhibitors (see language approved on Dec 4, 2015, DARRTS, reference ID 3856006), and language regarding drug-drug interaction potential for empagliflozin to inhibit UGT1A3, 1A8, 1A9 and 2B7 are proposed.

The sponsor had conducted Study n00234868-01 to determine the IC_{50} values for the inhibition of UGT1A3, UGT1A8, UGT1A9 and UGT2B7 by empagliflozin and assess its drug-drug interaction potential. Pooled human liver microsomes (HLM) were used for the determination of IC_{50} values for inhibition of UGTs by empagliflozin.

The sponsor assessed the inhibition potential of empagliflozin towards four UGTs. The IC_{50} values for all UGT substrates were greater than 100 μM, as shown in the Table 1 below:

Table 1 Empagliflozin IC_{50} and K_i Values

UGT	IC_{50} [1] (μM)	K_i [2] (μM)
rUGT1A3	>100	>50
UGT1A3 (in HLM)	>100	>50
rUGT1A8	>>100	>>50
UGT1A9 (in HLM)	>100	>50
UGT2B7 (in HLM)	>>100	>>50
UGT2B7 (in HLM) with BSA	>>100	>>50

1. Experiments were conducted at two separate occasions; n=3 for each experiment

2. Competitive inhibition was assumed and K_i value was calculated as $IC_{50}/2$, since the concentration of substrate was equal to the apparent K_m value.

The sponsor followed the EMA 2012 DDI guidance[1] to assess the UGT related DDI potential of empagliflozin. This guidance recommends an *in-vivo* DDI study for an enzyme with marked abundance in enterocytes if the [I]/Ki≥10, where [I] is the maximum dose taken at one occasion/250 mL. For enzymes in the liver, or in organs exposed to the drug through the systematic circulation, an in-vivo DDI study is recommended if the [I]/Ki≥0.02, where [I] is the unbound mean C_{max} obtained at the highest recommended dose. *Though the Agency's DDI guidance[2] does not have this criteria for UGT related DDI studies, similar recommendation is given for CYP related DDI studies. The criteria that the sponsor followed appears scientifically reasonable keeping in perspective high K_i values of empagliflozin for UGT inhibition from the in vitro studies, and is thus acceptable.* The sponsor used the total C_{max} for completeness of the evaluation. A summary of the DDI potential for empagliflozin is shown in Table 2.

[1] Guideline on the investigation of drug interactions. Committee for Human Medicinal Products (CHMP), European Medicines Agency, CPMP/EWP/560/95/Rev. 1 Corr.2, 21 June 2012, located at *http //www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf*

[2] Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, located at *http //www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf*

Table 2 Assessment of drug-drug interaction potential for empagliflozin

UGT	K_i (µM)	[a] $[I]_{gut}/K_i$	[b] C_{max}/K_i	[b,c] $C_{max,unbound}/K_i$	Potential for DDI
rUGT1A3	>50	<4.4	<0.014	<0.002	Remote
UGT 1A3 (in HLM)	>50	<4.4	<0.014	<0.002	Remote
rUGT1A8	>>50	<4.4	<0.014	<0.002	Remote
UGT 1A9 (in HLM)	>50	<4.4	<0.014	<0.002	Remote
UGT 2B7 (in HLM)	>>50	<4.4	<0.014	<0.002	Remote
UGT 2B7 (in HLM) with BSA[d]	>>50	<4.4	<0.014	<0.002	Remote

[a] EMA DDI criteria for an enzyme with marked abundance in enterocyte: an in-vivo DDI study is recommended if the $[I]_{gut}/K_i \geq 10$ where $[I]_{gut}$ is the maximum dose taken at one occasion/250 mL
[b] EMA DDI criteria for enzymes in the liver, or in organs, exposed to the drug through the systematic circulation: an in-vivo DDI study is recommended if the $[I]/K_i \geq 0.02$ where [I] is the unbound mean C_{max} obtained at the highest recommended dose. For completeness of the evaluation, the total C_{max} was also used for assessment.
[c] DDI was assessed using the unbound concentration (plasma protein binding=83.7%) [4]
[d] Assay was conducted in the presence of BSA (bovine serum albumin); other assays were conducted in the absence of BSA.

Reviewer Comments: *The sponsor states that based on the inhibition study described in report n00234868-01, the potential for DDIs between empagliflozin and concomitantly administered substrates of UGT1A3, UGT1A8, UGT1A9 and UG2B7 is considered remote. Based on the findings of the in vitro study, the sponsor concludes that in-vivo DDI studies are not required, and this reviewer is in agreement with sponsor's conclusion. Sponsor's suggested changes in Section 12.3 of the proposed PI under sub-heading "Drug Interactions", is acceptable.*

Changes to (b) (4) *of the proposed PI based on the findings of Study 1276.1 will be reviewed by the Medical Officer.*

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/s/

SURYANARAYANA M SISTA
02/11/2016

MANOJ KHURANA
02/11/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s005

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 204629/S-005

Application Type: Efficacy Supplement

Drug Name(s)/Dosage Form(s): Jardiance (empagliflozin) tablets

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Receipt Date: May 20, 2015

Goal Date: March 18, 2016 (PDUFA Date March 20, 2016)

1. Regulatory History and Applicant's Main Proposals

Empagliflozin is a selective inhibitor of sodium-dependent glucose co-transporter-2 (SGLT-2) and was developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Original IND 102145 was opened on April 10, 2008, to study empagliflozin as a treatment for type 2 diabetes. The End-of-Phase 2 meeting was held on January 21, 2010, and the Pre-NDA meeting was held on January 18, 2012. The new drug application for empagliflozin, NDA 204629, was submitted on March 5, 2013. The agency issued a Complete Response (CR) for the NDA on March 4, 2014, and a class 1 resubmission of the NDA was submitted on June 3, 2014. NDA 204629 for empagliflozin, proprietary name Jardiance, was approved on August 1, 2014.

Three prior approval efficacy supplements (S-001, S-002, and S-003), which proposed to add information to the Jardiance label from three corresponding clinical studies, were approved on June 26, 2015. A prior approval labeling supplement (S-004), which proposed the addition of results from a 10 week juvenile rat toxicology study conducted in fulfillment of PMR 2755-3, was approved on February 5, 2016.

On September 25, 2015, in conjunction with a Safety Labeling Change issued to SGLT-2 inhibitors for ketoacidosis and urosepsis, the agency concurrently issued a CR for a prior approval labeling supplement (S-006) that had proposed to add information about diabetic ketoacidosis. A prior approval supplement (S-007), submitted by the applicant in response to the Safety Labeling Change, was approved on December 4, 2015.

Two Chemistry Manufacturing and Controls (CMC) supplements, S-009 and S-010, were approved on January 11, and January 15, 2016, respectively.

In addition to S-005, which is the subject of this PLR format review, a prior approval efficacy supplement (S-008) is currently under review for its proposed new indication for reduced cardiovascular risk in diabetic patients based on the results of Study 1245.25 (EMPA-REG OUTCOME trial) which was conducted in fulfillment of PMR 2755-4. Additional supplements under

review include a CMC Changes Being Effected in 30 Days supplement (S-011) and a prior approval labeling supplement (S-012) which proposes the addition of text informing that fatal cases of ketoacidosis have been reported.

S-005 is a prior approval SE8 efficacy supplement that was submitted on May 20, 2015. It proposes to amend the Jardiance prescribing information with new information describing the results of Study 1276.1 entitled, "A 24-week phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug-naïve patients with type 2 diabetes mellitus." Additional changes proposed in this supplement include new text describing results of a UGT interaction study.

On March 3, 2016, the sponsor amended supplement S-005 to provided updated draft labeling following comments issued by the Agency on February 25, 2016. This March 3, 2016, sponsor's draft of the Prescribing Information is the version of the label reviewed below.

2. Review of the Prescribing Information

This review is based on the applicant's March 3, 2016, submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS**

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

YES 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *Revision date to be determined.*

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

YES 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *Safety altered first sentence ("The following" replaced with "Additional") and removed hyphen in "post-approval" in language added in prior class Safety Labeling Changes. Checked with Jenn Pippins (DMEP Deputy Director for Safety) and Monika Houstoun (DMEP*

Associate Director for Labeling) and we will leave as is. In the prior SLC approval letter, Safety had also changed "not always" to "generally."

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL G WHITE
03/07/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 2, 2016

To: Michael G. White, PhD, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204629/S-005
OPDP labeling comments for JARDIANCE® (empagliflozin) tablets, for oral use

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On June 26, 2015, OPDP received a consult request from DMEP to review an efficacy supplement regarding the proposed draft Prescribing Information (PI) for JARDIANCE® (empagliflozin) tablets, for oral use (Jardiance). OPDP's comments on the proposed draft labeling are based on the version sent by Michael White via email on February 25, 2016, and are marked on the version provided directly below.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

35 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARUNI P SHAH
03/02/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204629 SUPPL # 005 HFD # 510

Trade Name Jardiance

Generic Name empagliflozin

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known March 18, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 204629 Jardiance (empagliflozin) tablets

NDA# 206073 Glyxambi (empagliflozin and linagliptin) tablets

NDA# 206111 Synjardy (empagliflozin and metformin hydrochloride) tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 1276.1 A 24-week phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug-naïve patients with type 2 diabetes mellitus.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 1276.1 A 24-week phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug-naïve patients with type 2 diabetes mellitus.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 102145 YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Michael G. White, Ph.D.
Title: Regulatory Project Manager

Date: March 3, 2016

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL G WHITE
03/18/2016

JEAN-MARC P GUETTIER
03/18/2016